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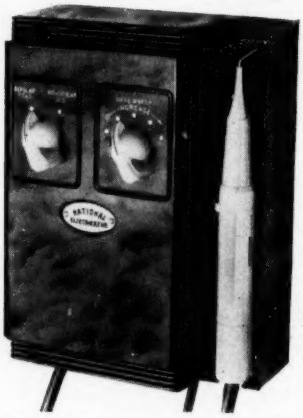

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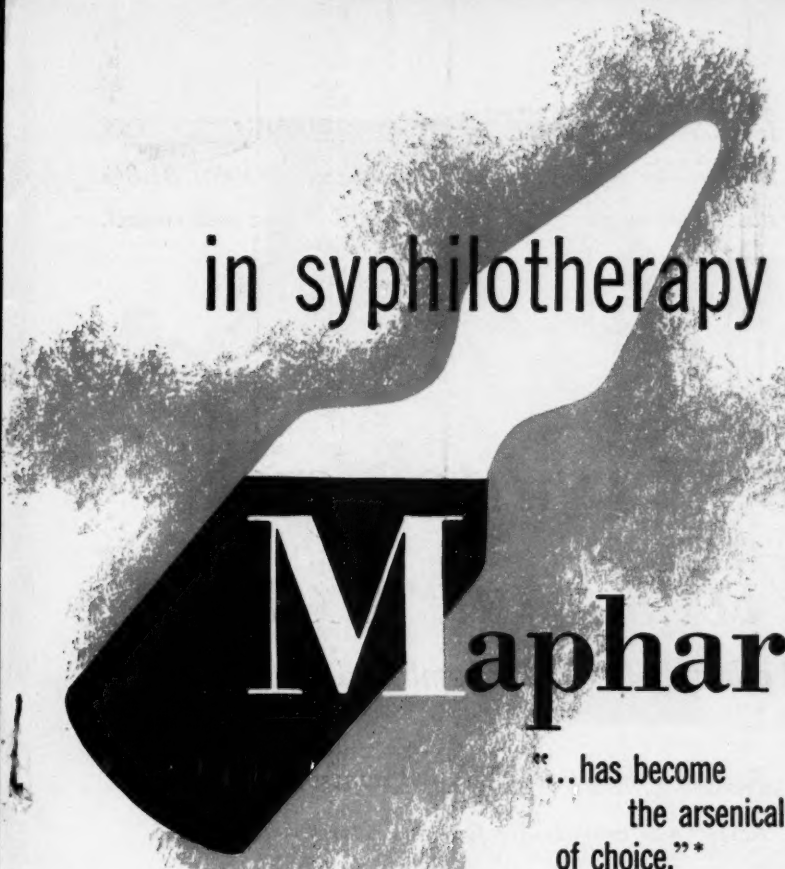

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*Harrison, T. R.: *Principles of Internal Medicine*, Philadelphia, The Blakiston Company, 1950, p. 981

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1. Stokes, J. G.: GP, 2:33, Aug., 1950.

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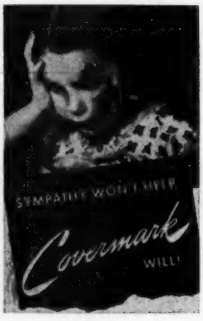

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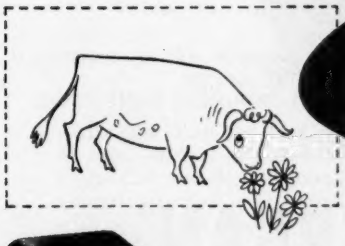

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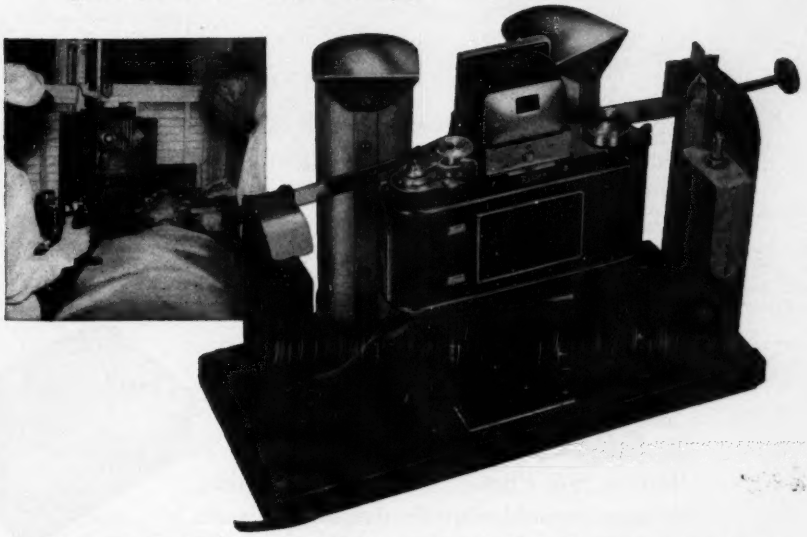

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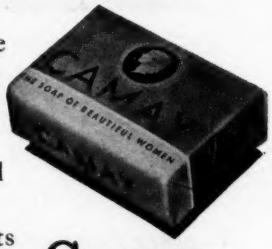

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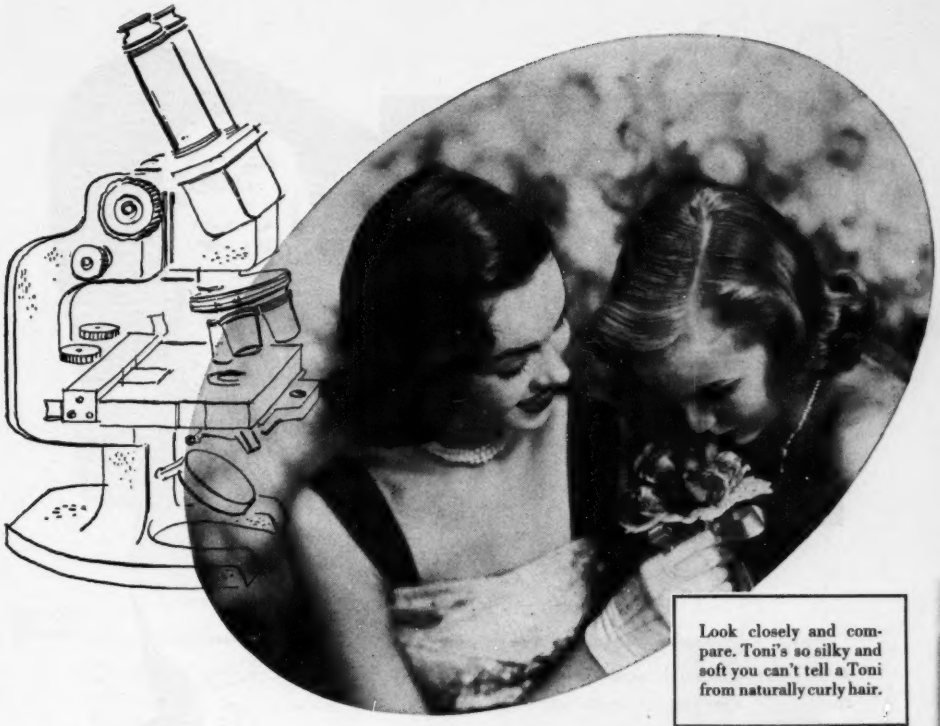

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*References: Behrman, H. T.; Combes, F. C.; et. al. The Cold Permanent Hair-Waving Process; A Dermatologic and Clinical Study J. A. M. A. 140: 1208 (Aug. 13, 1949). Reprints available on request.

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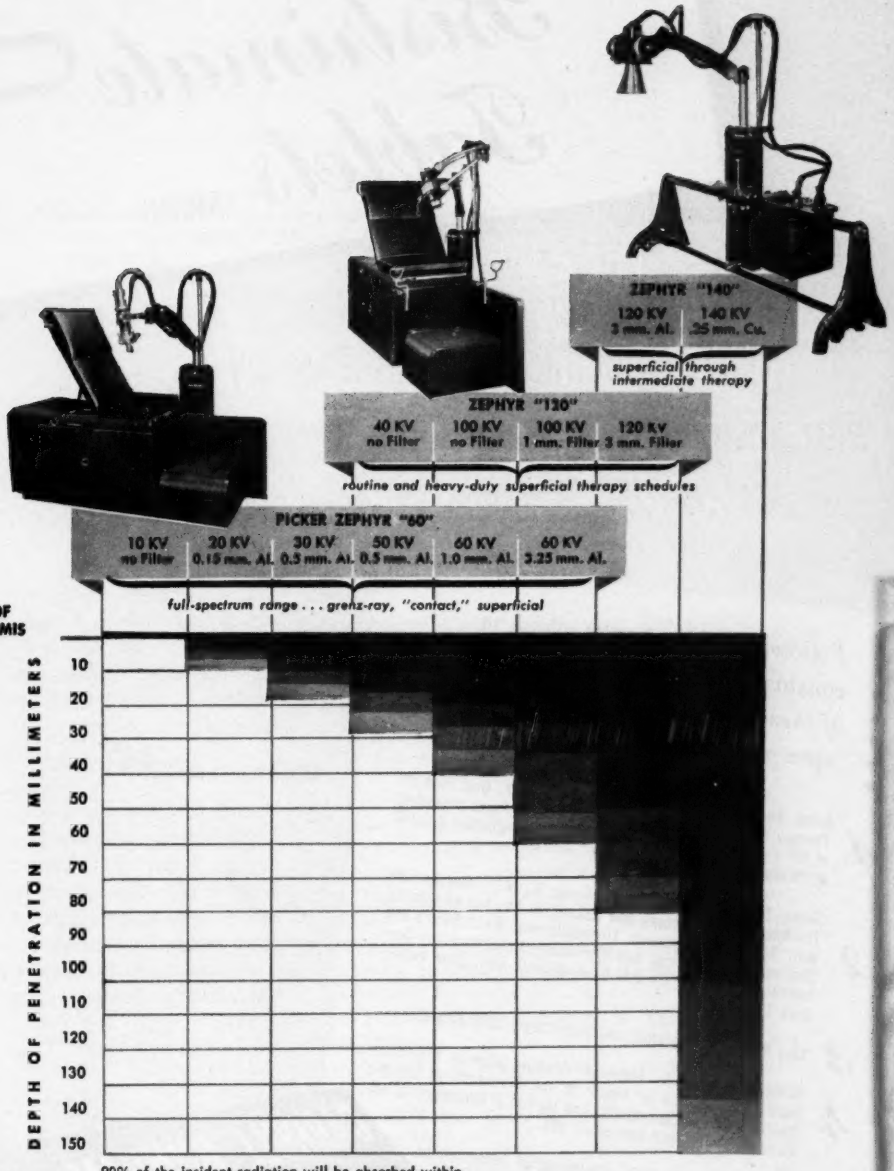

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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

6 Pascher, Frances, M.D.; Sawicky, H. H., M.D.; Silverberg, M.G., M.D.; and Emmet, Richard, M.D.; Bistrimate for Lupus Erythematosus, Lichen Planus and other Dermatoses. Journal of Investigative Dermatology, vol. 10, #6, June 1948.

7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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A. M. A.
Archives of Dermatology and Syphilology

VOLUME 63 JUNE 1951 NUMBER 6

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PROGESTERONE THERAPY IN DERMATOSES OF PREGNANCY (HERPES GESTATIONIS)

CORINNE KEATY, Ph.D.
PHYLLIS E. JONES, M.D.
AND
JOHN H. LAMB, M.D.
OKLAHOMA CITY

THE INCIDENCE of pruritic polymorphic eruptions during pregnancy or in the puerperium is not very great, but the condition occurs with sufficient frequency to warrant study, especially since the hazard is great for the fetus.

Herpes gestationis, the name suggested by Milton,[1] is the term generally employed today and does describe certain forms of the disease in which the chief characteristic lesion is herpetic. Allen[2] used the term dermatitis multiformis gestationis, and Brocq[3] employed the terminology *dermatite polymorphe douleureuse récidivante de la grossesse,* both of which names are perhaps more descriptive.

The greater proportion of the patients included in this study were seen early in the disease, when the symptoms were mainly pruritus, either localized or generalized. Early lesions, which were sometimes few, were small, erythematous papules and vesicles, initially 1 to 2 mm. in diameter, appearing in groups similar to grouping of lesions in dermatitis herpetiformis. Secondary infections were occasionally observed. The sites of predilection for the vesicles and papules were the upper portion of the buttock, the back, the lower legs, the abdomen and the forearms. In two instances the excoriated vesiculobullae with pigmentation resembled dermatitis herpetiformis. Lesions of the purely herpetic or bullous type were not observed in the majority of the patients. Only one patient presented lesions of the pemphigoid type. These were large flaccid bullae, many of which ruptured, leaving numerous large, raw areas. The study of this patient, as well as of one other in this group, was made possible through the courtesy of Dr. C. W. Lane of St. Louis.

It is well recognized that these skin lesions may exhibit a tendency to recur with increased severity in successive pregnancies, with grave prognosis for the patient and the fetus. This is particularly true when the onset is in the later

Read before the Section on Dermatology and Syphilology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 30, 1950.

1. Milton, J. L.: The Pathology and Treatment of Diseases of the Skin, London, R. Hardwicke, 1872, p. 205.

2. Allen, C. W.: Dermatitis Multiformis Gestationis, J. Cutan. & Genito-Urin. Dis. **7:** 291-296 (Aug.) 1889.

3. Besnier, E.; Brocq, L., and Jacquet, L.: La pratique dermatologique: traité de dermatologie appliqué, Paris, Masson & Cie, 1900, vol. 1, p. 688.

stages of pregnancy.[4] The disease is known to persist into the puerperium and more rarely may have its onset after delivery. In the latter condition, secretory activity of retained placental tags has been suggested as a causative agent.[5] When the onset is in early pregnancy the dermatosis may be transitory or may persist with greater or less intensity until delivery or later.

The time relationship of the onset of the disease to the sequence of profound hormonal changes of pregnancy is possibly significant. The appearance of the skin lesions in early pregnancy is generally at the time when the secretory activity of the chorioplacental system is confined largely to the production of chorionic gonadotropin and the normal blood and urinary titers of this hormone are extremely high. At this time placental production of steroids is at a comparatively low level, and the corpus luteum of pregnancy is functional and necessary for the maintenance of gestation in the human being. This first trimester peak in chorionic gonadotropin, according to Browne and Venning[6] and Evans and his co-workers,[7] lies about the fifty-second to sixty-fourth days and falls off considerably after the sixty-seventh day. There is a secondary rise again late in the last month of the third trimester, with subsequent absence of the hormone after the first few days post partum (72 to 96 hours).[8]

Estrogen production begins to increase at the time of the first fall in chorionic gonadotropin and progresses slowly, the greatest peak in production being about the thirty-eighth week. There is a decrease immediately prior to the onset of labor.[9] The curve of placental production of progesterone, as measured by pregnandiol excretion, in general parallels that of the production of estrogen.[10] Probably the greatest incidence of dermatoses in pregnancy is in the third trimester, when steroid production by the chorioplacental system is greatest, or post partum, when these substances rapidly decrease to the nonpregnant levels. There is a greater lag in the fall in gonadotropin.

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4. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners, with Revision of the Histopathology in This Edition by Clark Wylie Finnerud, ed. 4, Philadelphia, Lea & Febiger, 1934.

5. Turner, S. J., and Zakon, S. J.: Herpes Gestationis, Am. J. Obst. & Gynec. **41**:525-527 (March) 1941.

6. Browne, J. S. L., and Venning, E. H.: The Assay of Urinary Oestrin and Gonadotropic Substances During Pregnancy, Am. J. Physiol. **116**:18 (June) 1936.

7. Evans, H. M.; Kohls, C. L., and Wonder, D. H.: Gonadotropic Hormone in Blood and Urine of Early Pregnancy: Normal Occurrence of Transient Extremely High Levels, J. A. M. A. **108**:287-289 (Jan. 23) 1937.

8. (*a*) Smith, O. W., and Smith, G. V.: Prolan and Estrin in the Serum and Urine of Diabetic and Nondiabetic Women, with Especial Reference to Late Pregnancy Toxemia, Am. J. Obst. & Gynec. **33**:365-379 (March) 1937. (*b*) Siegler, S. L.: Estrogenic and Chorionic Gonadotropic Hormone in Normal Pregnancy and in Toxemia of Pregnancy, J. Lab. & Clin. Med. **24**:1277-1281 (Sept.) 1939.

9. Smith, G. V., and Smith, O. W.: Estrogen and Progestin Metabolism in Pregnancy: Endocrine Imbalance of Preeclampsia and Eclampsia; Summary of Findings to February, 1941, J. Clin. Endocrinol. **1**:470-476 (June) 1941.

10. Hamblen, E. C.; Cuyler, W. K., and Baptist, M.: Pregnanediol Determinations in Gynecology and Obstetrics, Am. J. Obst. & Gynec. **44**:442-454 (Sept.) 1942.

Quantitative imbalance in production or metabolism of the hormones of pregnancy is believed to be related to certain complications of pregnancy. Increased levels of chorionic gonadotropin in late pregnancy have been found to be associated with decreased placental production (or metabolism) of steroids in the toxemias.[11] Such hormonal imbalances have been corrected by substitutional therapy with

Fig. 1 (case 4).—The patient had had five previous pregnancies, with fetal loss in three. A vesiculobullous multiform eruption may be observed between the thighs, with coalescence and rupture of bullae, leaving a crusted, exudative surface. This was curable with progesterone for two months, but during the last trimester the eruption recurred even with the administration of 50 mg. daily, although it was not as severe then as when no treatment was given. The administration of testosterone, 50 mg. twice weekly, in addition, caused extreme exacerbation.

11. (*a*) Footnote 8. (*b*) Smith, G. V., and Smith, O. W.: Excessive Anterior-Pituitary-like Hormone and Variations in Oestrin in the Toxemias of Late Pregnancy, Proc. Soc. Exper. Biol. & Med. **30**:918-919 (April) 1933. (*c*) Browne, J. S. L.; Henry, J. S., and Venning, E. H.: The Significance of Endocrine Assays in Threatened and Habitual Abortion, Am. J. Obst. & Gynec. **38**:927-955 (Dec.) 1939.

rather impressive results.[12] However, direct evidence of a relationship between abnormal hormonal changes in pregnancy and the appearance and course of dermatoses in the pregnant state is lacking, although this has been suggested by certain authors.

Fig. 2 (case 4).—Eruption over the flexor surface of the arms, similar to that shown in figure 1.

12. (*a*) Smith, G. V., and Smith, O. W.: Excessive Gonad-Stimulating Hormone and Subnormal Amounts of Oestrin in the Toxemias of Late Pregnancy, Am. J. Physiol. **107:** 128-145 (Jan.) 1934. (*b*) White, P., and Hunt, H.: Pregnancy Complicating Diabetes: Report of Clinical Results, J. Clin. Endocrinol. **3:**500-511 (Sept.) 1943. (*c*) Smith, G. V., and Smith, O. W.: Observations Concerning the Metabolism of Estrogens in Women, Am. J. Obst. & Gynec. **36:**769-786 (Nov.) 1938. (*d*) White, P.; Titus, R. S.; Joslin, E. P., and Hunt, H.: Prediction and Prevention of Late Pregnancy Accidents in Diabetes, Am. J. M. Sc. **198:**482-492 (Oct.) 1939. (*e*) White, P., and Hunt, H.: Prediction and Prevention of Pregnancy Accidents in Diabetes, J. A. M. A. **115:**2039-2040 (Dec. 14) 1940. (*f*) Smith, O. W.; Smith, G. V., and Hurwitz, D.: Increased Excretion of Pregnanediol in Pregnancy from Diethylstilbestrol with Special Reference to the Prevention of Late Pregnancy Accidents, Am. J. Obst. & Gynec. **51:**411-415 (March) 1946. (*g*) Smith, O. W., and Smith, G. V. S.: Use of Diethylstilbestrol to Prevent Fetal Loss from Complications of Late Pregnancy, New England J. Med. **241:** 562-568 (Oct. 13) 1949.

It was thought that an evaluation of the blood chorionic gonadotropin levels in women with dermatoses of pregnancy might be of some significance and provide a rationale for therapy. Further interest in this problem was stimulated by similar studies being carried out at the University of Oklahoma School of Medicine on toxemia of diabetic pregnancy.[13] Accordingly, in May 1947 assays were begun on the blood of patients with herpes gestationis by a modification of the method described by White and her co-workers.[12d] Whole unprecipitated serum was used, since control studies in this laboratory had previously shown that identical results were obtained with untreated and treated blood serum. Immature female rats (Sprague-Dawley) aged 21 to 23 days and weighing 40 to 46 Gm. were used as the test animals. The unitage of chorionic gonadotropin of each blood sample was quantitated by dilution. The presence of corpora lutea in the immature rat ovary was used as the assay end point. Values were reported as units per 100 ml. of whole blood (two times the serum unit). Normal values for late pregnancy by this method have been found to range from 500 to 750 units, and elevation above 750 units was considered abnormal. At the time of writing, 10 patients with

TABLE 1.—*Pertinent Data from Previous Histories in Ten Cases*

Patient no.	1	2	3	4	5	6	7	8	9	10	Total
Abnormal menstruation	+	..	..	..	+	..	..	+	..	..	3
No. of previous pregnancies	3	1	3	5	1	..	..	..	5	2	20
No. of fetal losses	1	..	1	3	..	..	..	..	1	..	6 (30%)
Therapeutic abortion	..	..	..	..	..	..	..	..	..	+	1
Prematurity	..	..	..	..	..	..	..	..	1	..	1
Dermatosis	..	+	..	+++	+	..	..	..	+	+	7 (35%)
Trimester of onset	..	2	..	1; post partum	2	..	..	..	..	3; post partum	

dermatoses of pregnancy had been studied by this procedure. In addition, urinary 17-ketosteroid excretion was determined in four patients. The method of Robbie and Gibson[14] was used.

During the years 1947 to 1950, 11 patients presenting the dermatosis were seen, 10 of whom were studied (table 1). There were three primiparas in the group. The average age of the 10 patients was 29.1 years, the range being 21 to 40 years. The menstrual histories were considered abnormal in three instances, and the average age at menarche was 14 years. There had been a total of 20 previous pregnancies among these patients, which had terminated in 14 living children. The incidence of fetal loss was high (30 per cent), this loss having occurred six times in the course of 20 pregnancies, and three times in the same person. There had been one premature delivery among the successful pregnancies, and one instance of threatened abortion with delivery at term.

Four of the 10 patients had experienced moderate to severe skin lesions with previous pregnancies. Seven of the 20 previous pregnancies (35 per cent) had been characterized by the eruption. The onset had been early in the majority of patients; however, in two instances the lesions had appeared post partum (table 1).

13. Keltz, B. F.; Keaty, E. C., and Hellbaum, A. A.: Hormonal Studies in Diabetic Pregnancies, South. M. J. **43**:803-814 (Sept.) 1950.

14. Robbie, W. A., and Gibson, R. B.: Rapid Clinical Determination of Urinary 17-Ketosteroids, J. Clin. Endocrinol. **3**:200-205 (April) 1943.

During the pregnancies under consideration the onset was in late pregnancy in the majority of subjects; in only two was the onset in the first trimester. In one patient the eruption appeared 24 hours post partum. This patient had a history of previous occurrence of a dermatosis in the puerperium.

The clinical observations on these patients are of considerable interest. Five of the 10 women (50 per cent) had moderate to severe edema. Persistent headache had characterized one of the pregnancies, and hypertension, another. Four of the patients had albuminuria, and red blood cells were found in the urine of one other patient. Creatine excretion was normal for the pregnant state (an average of 290.065 mg. per 24 hours). Urinary 17-ketosteroid excretion was determined in only four patients and found to be within the lower limits of normalcy, averaging 7.75 mg. per 24 hours (normal, 5 to 15 mg.).

Since high titers of chorionic gonadotropin during the first trimester are physiologically normal, only the values for the later stages of pregnancy will be considered. In the eight patients in whom the disease had first appeared during the

TABLE 2.—*Principal Complaints During Pregnancies Included in Study and Average Amounts of Chorionic Gonadotropin During Specified Month of Pregnancy with Dose of Progesterone per Day*

Patient no.	1	2	3	4	5	6	7	8	9	10
Onset month of pregnancy	9	5	5	2	4	8	2	9	5	Post partum
Edema	..	..	+	..	..	+	..	+	+	+
Albuminuria	+	..	..	..	..	..	+	+	+	..
Red blood cells in urine	+	..	..	..	..	..	..	+	..	..
Hypertension	..	..	..	..	..	+	..	..	..	..
Headache	..	..	+	..	..	..	..	..	..	..
Therapeutic abortion	..	..	..	+(2)	..	..	..	..	..	..
Amount of chorionic gonadotropin with month of determination	2,000 (9)	1,000 (5)	7,000 (5)	1,000 (4)	2,000 (4)	3,000 (9)	1,500 (2)	4,000 (9)	2,000 (5)	500 (Post partum)
Dose of progesterone, mg. per day	75-50	25	25	50	50	12.5	25	75-50	25	60-50

late second or third trimesters, the average blood level of the gonadotropin was 3,125 rat units per 100 ml. of whole blood, a decided elevation over the normal level for the later stages of pregnancy (500 to 750 rat units per 100 ml.). However, assays above 500 units could not be obtained from the blood of the patient who had experienced postpartum onset of the dermatosis (table 2).

Since the demonstration of excess chorionic gonadotropin in later stages of pregnancy has previously been shown to be associated with decreased production or aberrant metabolism of progesterone,[15] it was felt that substitutional therapy with progesterone should be given a trial. As soon as blood (and in several instances also 24-hour urine) samples were obtained, parenteral treatment with crystalline progesterone (proluton®) [16] was begun. If the therapy was adequate—that is, if sufficient doses were maintained without irregularity in administration—the response was rapid and complete remission resulted. Early in the study in 1947 comparatively small doses were employed (12.5 to 25 mg. daily), but it was soon

15. (*a*) Footnote 11 *b* and *c*. (*b*) Browne, J. S. L.; Henry, J. S., and Venning, E. H.: Urinary Excretion of Prolan, Estrin and Pregnanediol in Normal Pregnancy and Late Pregnancy Toxemias, J. Clin. Invest. **17**:503, 1938. (*c*) Lu, C. S.: Total 24-Hour Urinary Excretion of Estrogens in Normal and Toxemic Pregnancies, Chinese M. J. **59**:131-142 (Feb.) 1941.

16. Dr. W. Alan Wright of the Schering Corporation provided the proluton® used in this study.

evident that large doses were necessary (50 to 100 mg. daily), until the response was well established and the skin significantly improved, after which time 25 to 50 mg. daily generally sufficed to maintain the remission. Withdrawal of treatment occasionally resulted in recurrence, which, in each instance, responded to further intensive treatment. The same procedure in treatment was used for patients with early or postpartum onset. It is of interest that there was postpartum recurrence in one patient who was receiving diethylstilbestrol for the inhibition of lactation. This recurrence was again controlled by the administration of progesterone. The requirements cannot be met satisfactorily with adminstration of the orally active form of progesterone, since its potency is about one-fifth that of the preparation for intramuscular injection.

At the time of writing, delivery had occurred in all 10 cases. All pregnancies proceeded to term except in one case, in which the patient was delivered prematurely in the eighth month. The infant survived. Cesarean section was done in one instance for cephalopelvic disproportion after prolonged labor. All the babies were in good condition, and there were no congenital anomalies. There were five boys and

TABLE 3.—*Outcome of Pregnancy in the Ten Cases*

Patient no.	1	2	3	4	5	6	7	8	9	10	Total
Delivery at term	+	+	..	+	+	+	+	+	+	+	9
Premature birth (month)	..	..	+ (8)	..	..	..	..	..	..	..	1
Spontaneous birth	+	+	+	+	+	+	+	..	+	+	9
Cesarean section	..	..	..	..	..	..	..	+	..	..	1
Boy	+	+	..	..	+	..	+	+	..	..	5
Girl	..	..	+	+	..	+	..	..	+	+	5
Fetal survival	+	+	+	+	+	+	+	+	+	+	10

five girls. There were no skin lesions among these infants, although one later had food allergy (table 3).

COMMENTS

Abnormal changes in the production and metabolism of the hormones of pregnancy in the toxemias have been the subject of intensive study. However, there are certain controversial aspects of the problem which still remain to be clarified. A common laboratory observation has been the occurrence of abnormally elevated levels of chorionic gonadotropin during the later stages of pregnancy.[17] However, a clearly delineated correlation between this observation and the incidence of toxemia

17. (*a*) Footnote 11. (*b*) Footnote 12 *a* and *b*. (*c*) Browne, Henry and Venning.[15b] (*d*) Taylor, H. C., Jr., and Scadron, E. N.: Hormone Factors in Toxemias of Pregnancy, with Special Reference to Quantitative Abnormalities of Prolan and Estrogens in Blood and Urine, Am. J. Obst. & Gynec. **37**:963-985 (June) 1939. (*e*) Smith, O. W.; Smith, G. V., and Hurwitz, D.: Relationship Between Hormonal Abnormalities and Accidents of Late Pregnancy in Diabetic Women, Am. J. M. Sc. **208**:25-35 (July) 1944. (*f*) Cohen, H. M.; Wilson, D. A., and Brennan, W. F.: Blood Gonadotropic Determinations in Relation to Toxemia of Pregnancy, Pennsylvania M. J. **46**:1282-1285 (Sept.) 1943. (*g*) Watts, R. M., and Adair, F. L.: Excretion of Estrogen and Gonadotropin in Late Pregnancy, with Especial Reference to the Toxemias of Pregnancy and to Quantitative Methods, Am. J. Obst. & Gynec. **46**:183-207 (Aug.) 1943.

and fetal mortality has not had complete confirmation.[18] Some of the discrepancies in the observations may be due to the fact that various assay methods have been employed by the different laboratories. Associated with the increased titers of chorionic gonadotropin in a large proportion of the patients there has been reported decreased production of progesterone and estrogen. This was observed in the majority of the patients studied by Browne, Henry and Venning,[19] Lu [15c] and the Smiths.[20] The data with reference to decreased progesterone production (or metabolism), as indicated by excretion of sodium pregnandiol glucuronidate, have constituted the more consistent and possibly the more significant observations.

Substitutional therapy with progesterone and estrogen has been employed in toxemic patients with varying degrees of success [21] and has been found to be effective as a preventive, not as a curative, measure in toxemia. Certainly the fetal mortality has been greatly reduced by steroid therapy in such patients, although the value of diethylstilbestrol in implementing increased production of progesterone is as yet questionable.[22]

A relationship between hormones and the occurrence of the dermatosis in the pregnant state has been suggested in dermatological and obstetrical literature by such findings as the frequent occurrence of tetany associated with low amounts of blood calcium, persistent thymus and pituitary and other changes.[23] An etiology of toxic origin was proposed by Hebra,[24] Gellhorn,[25] Howard [26] and Crawford and Leeper.[27] The prognosis for the fetus is not good. Intrauterine death, miscarriage or prematurity and the incidence of fetal anomalies support the concept of toxic etiology.[28] In further support of this idea, the presence of albuminuria and of red

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18. Siegler.[8b] White and Hunt.[12b] Browne, Henry and Venning.[15b] Footnote 17 *d* and *f*.

19. Footnotes 11 *c* and 15 *b*.

20. Footnotes 11 *b* and 12 *a*.

21. Footnote 12 *a*, *b* and *e*.

22. Davis, M. E., and Fugo, N. W.: Effects of Various Sex Hormones on Excretion of Pregnandiol in Early Pregnancy, Proc. Soc. Exper. Biol. & Med. **65**:283-289 (June) 1947. Abarbanel, A. R.: Prognostic Value of Pregnanediol Excretion in Threatened Abortion, with Special Reference to the Effects of Diethylstilbestrol, J. Clin. Endocrinol. **8**:615 (July) 1948. Sommerville, I. F.; Marrian, G. F., and Clayton, B.: The Effect of Diethylstilbestrol Administration During Pregnancy upon the Urinary Excretion of Pregnanediol and Natural Oestrogens, J. Endocrinol. **6**:i (April) 1949.

23. von Leszczyński, R.: Klinische Beiträge zur Kenntniss der Pathogenese der Impetigo Herpetiformis, Arch. Dermat. u. Syph. **156**:102-121, 1928. Danisch, F.: Impetigo Herpetiformis bei postoperativer Tetanie und parathyreopriver Kachexie, Ztschr. Path. **38**:290-312, 1928. Friedmann, M.: Ein Fall von Impetigo herpetiformis, Arch. Dermat. u. Syph. **165**: 457-468, 1932. Bohnstedt, R. M.: Kasuistischer Beitrag zur Frage Impetigo herpetiformis und Tetanie, ibid. **169**:357-363, 1933. Carter, B., and Pearse, R. L.: Impetigo Herpetiformis Occurring During Pregnancy, Am. J. Obst. & Gynec. **33**:114-125 (Jan.) 1937.

24. Hebra: Herpes Impetiginiformis, Lancet **1**:399, 1872.

25. Gellhorn, G.: Eczema in Pregnancy, Am. J. Obst. & Gynec. **26**:408-412 (Sept.) 1933.

26. Howard, R. L.: Herpes Gestationis: Report of a Case, Arch. Dermat. & Syph. **28**: 782-789 (Dec.) 1933.

27. Crawford, G. M., and Leeper, R. W.: Diseases of the Skin in Pregnancy, Arch. Dermat. & Syph. **61**:753-772 (May) 1950.

28. Levigne, S.: Thesis, Paris, cited by Riecke, E., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, vol. 7, pt. 2, Berlin, Julius Springer, 1931. Bryan, C. A. D.: Recurrent Herpes Gestationis, Lancet **1**:512, 1906.

blood cells in the urine has been a rather consistent observation in these patients,[26] and retention of chloride, urea and total nitrogen has been reported by Perrin.[29] The previous history of a rather high incidence of fetal loss, 30 per cent in 20 pregnancies, in the patients reported here is significant. The edema, hypertension, threatened abortion and albuminuria which were observed in seven of the 10 pregnancies in these patients (70 per cent) is greater than the generally accepted incidence of manifest toxemia (about 8 per cent) in the general population, although the number of cases is much too small for the figures to be significant and none of the patients had all the classic signs of toxemia.

The observation of elevated chorionic gonadotropin titers in late pregnancy and the response to treatment with progesterone are suggestive of progesterone deficiency. In early pregnancy the normally high levels of the gonadotropin may be incriminated in the presence of inadequate amounts of progesterone. As early as 1924 Tommasi [30] attributed—or at least related—herpes gestationis to corpus luteum hormone deficiency and employed whole ovarian extracts in treatment of the disease with benefit. Essentially the same idea was held by Sechi [31] and Jordan,[32] both of whom used ovarian preparations with success. Perondi [33] also maintained that the disease had its origin in a hormonal deficiency. However, the earlier preparations were comparatively impotent with respect to progestational activity. Turner and Zakon [5] treated a patient with estrogen (estradiol benzoate [progynon® B], with a total dose of 600,000 units) and crystalline progesterone (prolution,® total dose of 70 mg.) over a period of seven days without influencing the course of the disease. In this instance the total dose of progesterone was comparatively small.

While the dermatosis is extremely rare as a complication of frank toxemia, the combination has been observed. Gilman [34] reported one such patient whose skin lesions underwent remission during the administration of progesterone. The patient of Kampf [35] who received progesterone (proluton®) for habitual abortion showed improvement of the complicating dermatosis. In discussion of Kampf's patient,[35] Rostenberg stated that he had observed one puerperal patient in whom secretion of chorionic gonadotropin was prolonged for several months after delivery. Elliot's report [36] of a patient with skin lesions of great severity associated with metastatic chorioma following the delivery of a hydatidiform mole is of great interest. The intensity of the dermatosis was correlated with the increasing secretory activity of the chorionic neoplasm as evidenced by the increasing titers of chorionic gonadotropin. The authors suggest that the quantitative Ascheim-Zondek test might be useful in instances of the postpartum occurrence of the bullous dermatoses of preg-

29. Perrin, C.: Herpes Gestationis, Ann. dermat. et syph. **5**:1370, 1894.

30. Tommasi, L.: Contributo alla conoscenza dell' herpes gestationis, Gior. ital. mal ven. **65**:840-882 (June) 1924.

31. Sechi, E.: Contributo alla studio dell' herpes gestationis, Gior. ital. dermat. e sif. **73**: 1353-1372 (Aug.) 1932.

32. Jordan, A.: Wie soll man die Dermatitis herpetiformis Duhring (D. h. D.) behandeln? Dermat. Ztschr. **68**:166-171 (Dec.) 1933.

33. Perondi, G.: Sulla patogenesi dell' "herpes gestationis," Clin. ostet. **27**:225-229, 1925.

34. Gilman, R. L., in discussion on Backus, C. C., and Stokes, J. H.: Dermatitis Herpetiformis and Herpes Gestationis, Arch. Dermat. & Syph. **27**:1003 (June) 1933.

35. Kampf, M. B.: Herpes Gestationis, Arch. Dermat. & Syph. **42**:982-983 (Nov.) 1940.

36. Elliott, J. A.: Bullous Dermatoses of Toxic Origin: Report of a Case Involving Association with Choriocarcinoma, Arch. Dermat. & Syph. **37**:219-233 (Feb.) 1938.

nancy, since prolonged production of chorionic gonadotropin may be due to residual placental tissue. However, the hormonal status of the one puerperal patient reported here in whom there was no abnormal elevation of gonadotropin must have another explanation. It is possible that the precipitating event may have been the sudden deprivation of the body of the plethora of hormones at delivery, although there is no proof whatever that this surmise is correct.

The relation of chorionic gonadotropin to etiology of skin lesions is unknown. Its significance may be indirectly interpreted as a correlate of decreased steroid production, which is more probable, or its definitive action may be direct, with the skin as the shock organ. In this respect, the evidence from the many investigations of the hormones of pregnancy as related to the toxemic state points to primary deficiency of steroids of the chorioplacental system. This etiologic theory has been borne out by the results of treatment based on the correction of abnormal hormonal imbalance. Clinical response of the dermatoses of pregnancy to steroid therapy and the presence of elevated chorionic gonadotropin levels during late pregnancy indicate a similar deficiency in patients with dermatoses during pregnancy.

SUMMARY

Ten patients with pruritic polymorphic eruptions during pregnancy were investigated. The onset of the disease had occurred during the first trimester of pregnancy in two instances, during late pregnancy in seven and 24 hours post partum in one. There had been a fetal mortality of 30 per cent and one premature delivery in the course of 20 previous pregnancies. Four of the 10 patients had experienced the dermatosis with previous pregnancies, it having occurred seven times in the 20 previous pregnancies (35 per cent).

During the pregnancy under consideration, 50 per cent of the patients had moderate to severe edema and four had albuminuria. Persistent headache, red blood cells in the urine and hypertension were observed in three patients. The level of blood chorionic gonadotropin in seven patients was abnormally elevated during late pregnancy, averaging 3,125 rat units per 100 ml. of blood (normal, 500 to 750 R. U.). Progesterone (proluton®), 25 to 50 mg. daily, was administered to patients with resultant remission of the skin lesions in all 10 patients. All 10 pregnancies terminated in living, normal infants. There was one instance of premature delivery at eight months with fetal survival.

John T. Keown provided technical assistance in carrying out the gonadotropin assays.

ABSTRACT OF DISCUSSION

DR. C. J. LUNSFORD, Oakland, Calif: Drs. Keaty, Jones and Lamb are to be congratulated on this needed study and excellent presentation of their results in the treatment of herpes gestationis with progesterone.

So far as I have been able to determine by reference to the literature, except for one case report, as cited by the authors, this is the first study of the administration of progesterone in such cases.

My associates and I, commenting on the rarity of this disease, agreed that none of us had seen a case of herpes gestationis for many years. I then discussed the incidence of this disease in the Bay area with many of the local dermatologists and obstetricians. They included those conversant with the skin diagnoses in the patients entering the University of California and Stanford University Hospital outpatient clinics. In the last decade only two cases in which

such diagnosis had been made were reported by those I interviewed. Without suggesting that this figure represents an accurate census of the number of cases of herpes gestationis I think it might speak for the rarity of the disease in northern California. The authors were fortunate in having for study 10 such cases in a period of three years. If the apparent difference in the incidence of the disease between northern California and Oklahoma is a fact, what is the explanation? Could it be a difference of opinion as to the criteria in establishing the diagnosis of herpes gestationis?

The authors of the paper I think clearly showed that the substitution therapy of progesterone in herpes gestationis was a reasonable procedure. In nine out of 10 such cases under study in late pregnancy they showed, by means of blood assays, an abnormal increase in chorionic gonadotropin. This, combined with the known decrease in progesterone in the toxemias of late pregnancy and spontaneous abortion, as indicated by the urinary tests for pregnandiol, made such substitution therapy as they used a logical one. The lack of proof that such hormonal imbalance is the cause of herpes gestationis, as noted by the authors, properly did not deter them from using such substitution therapy. Their complete clinical control of the disease in all 10 cases, plus the successful termination of the pregnancy in the eight patients who had come to term at the time of the writing of the paper, as expressed in healthy mothers and normal infants, certainly justified them in their use of such therapy.

The suspected carcinogenic properties of hormones, if considered by the authors, were properly ignored. As I interpret the literature, it is only the long-continued use of such hormones in large doses that might incite to carcinomatous changes. The short duration of therapy in the cases under study permitted the authors to ignore such possibilities.

In general one thinks that where therapy has been applied in only 10 cases of any disease the results of such treatment must be received with proper skepticism. The entirely satisfactory results obtained by the authors, however, speak for the possible specificity of the therapy used. Surely such extremely good results will stimulate others to a trial of the use of progesterone when they are faced with this disease.

Although here in northern California we see little of herpes gestationis we do occasionally see the pruritic, papular eruptions which persist about the vulva, upper part of the thighs and lower portion of the abdomen in pregnant women. Whether or not this is a variant of herpes gestationis, as suggested by Dr. E. J. Trow, it is stubborn to treatment. We are indebted to the authors of this paper for a fresh and perhaps efficient means of approach in the management of this distressing condition.

The data as presented in this paper should be of particular interest to those dermatologists who think of herpes gestationis as a variant of dermatitis herpetiformis. Progesterone, as suggested by Drs. Crawford and Leeper,[27] is probably a safer means of therapy than has previously been at their disposal in the treatment of Duhring's disease.

DR. HARRY L. ARNOLD JR., Honolulu, T. H.: I should like to thank the presenters for offering us something that appears to be so useful and effective in the management of this very intractable disease. I am reminded forcibly of many patients with it in whom I have been entirely unable to control the disease, and of one in particular in whom the usual complete postpartum recovery was followed by a very severe relapse some three or four weeks post partum, immediately on the obstetrician's giving her estrogenic hormone for the purpose of decreasing lactation. She became so ill that she had to be rehospitalized for the treatment of the relapse that was apparently thus produced.

DR. PHYLLIS E. JONES, Oklahoma City: I shall show a few slides to demonstrate the type of lesions present in our series of cases.

Generally we observed an erythematous, papular or papulovesicular eruption involving the extremities and also the face, chest, abdomen and back. Sometimes the lesions were mainly vesicular or bullous and grouped. In the severest case observed there was presented a generalized bullous eruption which developed during the second month of pregnancy. The patient had a history of a dermatitis during each of three previous pregnancies. The eruption began to clear almost immediately when treatment with progesterone was instituted, but a relapse occurred when the patient missed the injections for a few days. Improvement again resulted from progesterone therapy, but larger doses were required and the dermatitis was more difficult to control than before.

One patient presented grouped vesicular lesions on the upper parts of the thighs, the chest and the back, which resembled dermatitis herpetiformis. Another patient presented a papulovesicular eruption on the face, arms and legs with edema and redness of the feet and ankles and exfoliation in these areas.

Only one patient manifested lesions 24 hours post partum. She had grouped vesicular lesions on the arms, breasts and chest which cleared soon with the administration of progesterone. She gave a history of similar eruptions post partum with previous pregnancies.

We believe many of these cases may represent variations of dermatitis herpetiformis. Some persons presented lesions that would generally be diagnosed as characteristic of dermatitis herpetiformis.

I wish to point out that the first symptom which all these patients presented, and their chief complaint, was pruritus.

We were impressed with the rather dramatic relief of symptoms, noticed within 24 to 48 hours after institution of progesterone therapy. It is necessary to give adequate doses of progesterone (50 to 100 mg. daily) at regular intervals and to continue therapy until delivery or until symptoms are completely controlled.

Although this series was small it seems significant that to the time of our report there had been no fetal mortality.

Dr. Lunsford mentioned the carcinogenic factor. Progesterone has no known carcinogenic activity. In normal pregnancy the progesterone levels are very high, and so we would consider a high level of that hormone a physiological state in these cases.

I should like to mention, in regard to Dr. Arnold's remarks about relapse following use of estrogens, that we saw this happen also in one of our cases. This was later controlled by giving more progesterone, but the patient had been doing well until she was given estrogens following delivery.

I wish to thank the discussers for their kind remarks.

ANTIBIOTICS IN EARLY SYPHILIS AND IN SYPHILIS COMPLICATED BY PREGNANCY

HARRY M. ROBINSON, M.D.
AND
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THE RENEWED interest in syphilotherapy that began with Ehrlich, who at first believed that arsphenamine could eradicate syphilis with one injection, has continued with the hope that some such quick cure could be found. Pollitzer [1] and, in more recent years, Chargin [2] believed that by giving arsenical treatments daily for a few days or by administering large doses in a slow but continuous drip method one could obtain a cure. However, serious reactions due to intensive arsenical therapy were reported, and in a few instances death occurred.

When Mahoney and co-workers [3] reported that injections of penicillin were curative and caused no reactions, it was felt that the ultimate safe cure had been found. It was soon noted that the 600,000 units originally used was not sufficient for cure, and relapses were frequent. Even with the dose increased to 1,200,000 and 2,400,000 units, too many recurrences were noted. It should be remembered that the earlier penicillin contained the K fraction and was not as effective against syphilis as the present penicillin G. At present, with the amount used ranging from 3,000,000 to 10,000,000 units, penicillin is the antibiotic drug in favor.

From the Department of Dermatology, University of Maryland School of Medicine.

Read before the Section on Dermatology and Syphilology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 30, 1950.

Assistance was given us as follows: Sharp and Dohme, Inc., Glenolden, Pa., provided the entire supply of the three varieties of penicillin used and the carinamide. Dr. T. E. Woodward of the Department of Medicine furnished a portion of the chloramphenicol, terramycin and aureomycin used in this study. Parke-Davis & Company, Detroit, supplied chloramphenicol. Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., supplied aureomycin. Dr. F. R. McCrumb Jr., Dr. J. Hightower, Dr. Gerald Martin, Dr. B. Joslin, Dr. R. Bauer and Dr. K. Y. Swisher Jr. also assisted in this study. Credit is also due to the Department of Obstetrics for admitting those patients who were treated with penicillin tablets and penicillin in oil and wax.

1. Pollitzer, S.: The Principles of the Treatment of Syphilis, J. Cutan. Dis. **34**:633 (Sept.) 1916.

2. Leifer, W.; Chargin, L., and Hyman, H. T.: Massive Dose Arsenotherapy of Early Syphilis by Intravenous Drip Method: Recapitulation of Data (1933-1941), J. A. M. A. **117**:1154 (Oct. 4) 1941.

3. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**:355 (Dec.) 1943.

In 1948 O'Leary and associates [4] and Wiggall and associates [5] reported the disappearance of Treponema pallidum from surface lesions following the use of aureomycin. In 1949 Smadel and co-workers [6] used chloramphenicol in the treatment of gonorrhea and early syphilis and noted that T. pallidum disappeared from the surface lesions in 48 to 72 hours. Later that year Robinson and Robinson,[7] Olansky and associates [8] and R. C. V. Robinson and associates [9] reported the same phenomenon. In mid-1947 we undertook to evaluate all the current antibiotic drugs in the treatment of syphilis and to determine, if possible, the comparable value of each. Up to the present, we have treated 127 patients with penicillin, 14 with chloramphenicol, 20 with aureomycin and 5 with terramycin.

PENICILLIN

Purposes of Study

The portion of the study concerned with penicillin was initiated to determine the following points: (1) the value of a single dose of 300,000 units of penicillin in an absorption-delaying vehicle, given at weekly intervals over a 35 week period, in the treatment of early syphilis; (2) the percentage of patients who would report regularly and complete a prescribed course of therapy daily or weekly as outpatients, without cost to them; (3) the value of an absorption-delaying drug such as carinamide used concurrently with the injections of penicillin in the treatment of syphilis, and (4) effectiveness of penicillin in the form of buffered tablets, with or without carinamide, in the treatment of early syphilis or syphilis complicated by pregnancy.

Material and Methods of Study

Of the 127 patients treated with penicillin, 56 had dark field-positive lesions of early syphilis and 71 had syphilis complicated by pregnancy. Of the latter group, 7 had secondary mucocutaneous syphiloderms, 56 had early latent syphilis and 8 had late latent syphilis. Only primiparas or those who had had only one previous pregnancy were included in the pregnancy group. In it there were only three white patients and the age range was 15 to 43 years; in the group of persons with uncomplicated early syphilis the ages ranged from 2 to 59 years.

Ten different schedules of treatment with penicillin were used, as shown by table 1. Those in the pregnancy group for whom schedules G, H, I and J were employed were hospitalized during the course of therapy and were again hospitalized at the time of delivery. The number of

4. O'Leary, P. A.; Kierland, R. R., and Herrell, W. E.: The Oral Administration of Aureomycin (Duomycin) and Its Effects on Treponema Pallidum in Man, Proc. Staff Meet., Mayo Clin. **23**:574 (Dec. 8) 1948.

5. Wiggall, R. H.; Zheutlin, H. E. C.; Trice, R.; Elmendorf, D. F., Jr., and Robinson, R. C. V.: Studies on the Effect of Aureomycin on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **33**:416 (Sept.) 1949.

6. Smadel, J. E.; Bailey, C. A., and Mankikar, D. S.: Preliminary Report on the Use of Chloramphenicol (Chloromycetin) in the Treatment of Acute Gonorrheal Urethritis, J. Clin. Invest. **28** (pt. 1):964 (Sept.) 1949.

7. Robinson, H. M., and Robinson, H. M., Jr.: Studies on Chloromycetin in Early Syphilis and Gonorrhea, South. M. J. **42**:988 (Nov.) 1949.

8. Olansky, S.; Romansky, M. J.; Taggart, S. R., and Robin, E. D.: The Anti-Treponemal Effect of Oral Chloromycetin in 32 Cases of Early Syphilis in Man: A Preliminary Report, Science **110**:639 (Dec. 9) 1949.

9. Robinson, R. C. V.; Fox, L. M., and Duvall, R. C.: Effect of Chloramphenicol in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:509 (Nov.) 1949.

patients treated with each schedule was as follows: A, 13 patients; B, 23 patients; C, 7 patients; D, 7 patients; E, 6 patients; F, 42 patients; G, 11 patients; H, 9 patients; I, 4 patients, and J, 5 patients.

Results of Study

Early in the investigation it became apparent that carinamide did not enhance the curative effects of penicillin when administered concurrently with intramuscular injections of penicillin in oil and wax or with buffered penicillin tablets given orally;

Table 1.—*Ten Schedules Used in the Treatment with Penicillin of 127 Patients with Dark Field-Positive Early Syphilis and/or Syphilis Complicated by Pregnancy*

I. Primary and Secondary Syphilis
- A. 300,000 units of procaine penicillin in oil once weekly for 35 weeks (all treatments on an outpatient basis)
- B. 300,000 units of penicillin G in oil and wax once weekly for 35 weeks (all treatments on an outpatient basis)
- C. Same as schedule B, with 6.0 Gm. of carinamide given orally at the time of each dose
- D. 100,000 units of penicillin in buffered tablets given three times daily for 15 days on outpatient basis
- E. Same as schedule D, with 2.0 Gm. of carinamide with each dose

II. Syphilis Complicated by Pregnancy
- F. 300,000 units of procaine penicillin in oil daily for 15 days (all treatments on an outpatient basis)
- G. 300,000 units of penicillin in oil and wax daily for 15 days (all patients hospitalized for duration of treatment)
- H. Same as schedule G, with 6.0 Gm. of carinamide with each dose
- I. 100,000 units of penicillin in buffered tablets three times daily for 15 days (all patients hospitalized)
- J. Same as schedule I, with 2.0 Gm. of carinamide with each dose

Table 2.—*Patients with Uncomplicated Early Syphilis Treated with Penicillin*

Type of Treatment	Stage of Syphilis	No. of Patients	No. Who Completed the Course	No. Who Did Not Complete the Course	No. "Cured" *	No. Who Improved Under Observation †	No. Lost from Observation
Penicillin in oil and wax (schedules B and C)	Primary	9	2	7	2	1	6
	Secondary	21	3	18	10	0	11
Procaine penicillin in oil (schedule A)	Primary	4	1	3	1	1	2
	Secondary	9	2	7	1	5	3
Penicillin in buffered tablets (schedules D and E)	Primary	3	0	3	0	0	1
	Secondary	10	2	8	0	0	4
Total		56	10	46	14	7	27

* With involution of all lesions plus reversal of serologic reaction to negativity and negative cerebrospinal fluid reaction.
† With lesions healed and significant drop in serologic titer.

therefore, in the compilation of our results schedules B and C (penicillin in oil and wax) and schedules D and E (buffered penicillin tablets) will each be grouped together and discussed under one heading. This same procedure is used in discussion of the cases of syphilis complicated by pregnancy in which schedules G and H (penicillin in oil and wax) and schedules I and J (penicillin buffered tablets) were employed.

Uncomplicated Early Syphilis (table 2).—Thirteen patients were in the group of those scheduled to be given weekly injections of 300,000 units of procaine penicillin in oil for a 35 week course as outpatients. Only three of these patients completed the course, and of these two became seronegative and had negative

results on spinal fluid examinations six months after the treatment was ended. Six patients received from 16 to 30 treatments and improved under therapy in that there was a significant drop in the titer in the serologic test for syphilis. The remainder were transferred to a public health agency because of refusal to return to the clinic. Thirty patients were in the group scheduled to be treated with a weekly injection of 300,000 units of penicillin in oil and wax for 35 weeks. Five of these patients completed the course, and all five became seronegative in the required time. Although 25 of them did not complete treatment, 12 of this group became seronegative and had negative spinal fluid reaction six months later. Of the eight who did complete the 35 weeks scheduled course, seven had a negative reaction to the serologic test for syphilis and negative results on spinal fluid examination. Thirteen patients were in the group to be treated with buffered tablets, each containing 100,000 units of penicillin, given three times daily for 15 days. Two of these patients completed the course of treatment, but there was no reversal

TABLE 3.—*Data on Penicillin Therapy of Patients with Early Syphilis Complicated by Pregnancy*

Type of Treatment	Stage of Syphilis	No. of Patients	Month of Pregnancy at Start of Treatment							Outcome of Pregnancy		Effect on Mother's Syphilis	
			3	4	5	6	7	8	9	Normal Child	Child with Congenital Syphilis	Improvement	No Change
Procaine penicillin in oil (schedule F)	Primary or secondary	4	..	..	2	..	1	..	1	2	2	4	0
	Early latent	31	..	1	8	15	3	3	1	31	..	6	25
	Late latent	7	1	..	3	1	1	1	..	7	..	0	7
Penicillin in oil and wax (schedules G and H)	Primary or secondary	2	..	..	1	..	..	..	1	1	1	2	..
	Early latent	17	2	..	5	3	5	1	1	14	3	8	9
	Late latent	1	..	..	1	..	..	..	..	1	..	..	1
Buffered penicillin tablets (schedules I and J)	Primary or secondary	1	..	..	..	..	1	..	..	1	..	..	1
	Early latent	8	..	..	3	5	..	..	..	5	3	2	6
Total		71	3	1	23	24	11	5	4	62	9	22	49

of the serologic reaction to negative in either of them although all lesions healed. One of those who completed the course had an infectious relapse, manifesting condylomata lata two months after treatment was completed, and the other patient who completed treatment had a neurorelapse, with Bell's palsy, two months later.

Syphilis Complicated by Pregnancy (table 3).—There were 42 outpatients treated with 300,000 units of procaine penicillin in oil once daily for 15 days, and all but one of this group were regular in attendance and received the prescribed course. The one exception was at term at the time of admission and received only one injection before being delivered of a stillborn child the next day. One mother, who completed treatment at the seventh month, was delivered of a congenitally syphilitic baby. The remaining 40 pregnant patients of this group were delivered of full term living children. All these children were subsequently proved to be nonsyphilitic.

Twenty pregnant patients were treated with 300,000 units of penicillin in oil and wax once daily for 15 days, and all of this group were hospitalized for the duration of the course and for the delivery. One mother who had secondary syphilis and who was at term at the time of admission was delivered of a stillborn child after the fourth injection, and one woman who had completed treatment at the fifth

month had a miscarriage at the seventh month. One child, whose mother had completed treatment at the sixth month, had roentgenologic and serologic evidences of congenital syphilis. Ten of these mothers were benefited by the course of treatment, and 10 showed no change as gaged by the titer in the serologic test for syphilis.

Nine hospitalized pregnant patients were given 100,000 units of penicillin three times daily administered in buffered tablets. The children born of three of the mothers treated by this method were syphilitic. One of the women who had secondary syphilis at the time of admission and who completed the course of treatment was delivered of a normal infant who remained free of infection; three months later, the mother had an infectious relapse. The remaining five women were delivered of normal children.

CHLORAMPHENICOL

Previous Investigations.—Smadel and his co-workers [6] were the first to discover that the administration of chloramphenicol to patients with dark field-positive lesions of early syphilis would cause the disappearance of T. pallidum from surface lesions. They concluded that this drug is less effective than penicillin against the spirochete because in one of their two patients the results on dark field examination were still positive 18 hours after a single dose of 4 Gm. of chloramphenicol. In both of the patients they observed that the lesions healed very slowly, and both had relapses four and six weeks after treatment. In each case, however, the dose administered was small and treatment was not carried beyond the third day. Robinson, Fox and Duvall [9] reported a series of 17 cases of primary or secondary syphilis which they treated with chloramphenicol. They administered 1 Gm. every six hours to a total of 40 Gm. In one of their patients lesions were dark field negative for T. pallidum after 24 hours; in the other 16, the dark field examinations gave negative results in from 30 to 50 hours. They carried out in vitro experiments and concluded that chloramphenicol was not treponemicidal in vitro but advanced the theory that it may exert its action by inhibiting the reproduction of the organisms. They believed that the necessity of giving multiple oral doses would tend to make this drug of little practical value in the treatment of syphilis. We [7] reported the effect of chloramphenicol in the treatment of five patients with dark field-positive lesions of early syphilis and found that the T. pallidum disappeared from the moist lesions in 24 to 48 hours after the administration of the initial dose of the drug. It was our opinion that the early lesions healed rapidly, but at the time of that report the period of follow-up and the size of the series of cases were not sufficient to warrant any statement as to the effects of chloramphenicol on the future course of the disease.

Since then, we have studied nine additional cases, two of which were of dark field-positive early syphilis complicated by pregnancy. This report will include the follow-up studies on the original five cases plus data on the nine additional patients as well as a preliminary statement on the effect of chloramphenicol in the treatment of early syphilis complicated by pregnancy.

Material and Methods of Present Study.—The study on chloramphenicol was conducted as follows:

Observations were made on 14 patients with dark field-positive lesions of early syphilis who were admitted to the University of Maryland Hospital for treatment with chloramphenicol. The

TABLE 4.—*Chloramphenicol in the Treatment of Early Syphilis*

Case No.	Patient's Age, Race, Sex	Manifestation	Total Dose, Gm.	Time Before Negative Dark Field Observations, Hours	Healing Time of Lesions, Days	Serologic Titer Before Treatment	Serologic Titer Six Mo. After Treatment	Cerebrospinal Fluid Reaction	Reactions to Chloramphenicol	Comments
1	17, N, F	Multiple chancres of breasts	15	24	7	64	4	0	0	.....
2	19, N, F	Condylomata lata; pregnancy of 7½ months	48	24	14	64	0	..	0	Normal child
3	21, W, F	Papular syphilis; condylomata lata	48	24	11	64	0	0	0	Reinfection 1-3-50
4	24, N, F	Condylomata lata	48	24	5	64	4	0	0	Normal child; sero-relapse
5	49, W, M	Chancre	3	48	11	16	0	0	0	.....
6	27, N, F	Chancre of nipple	48	24	14	1	0	0	0	.....
7	24, W, M	Chancre	48	36	14	0	0	0	0	.....
8	55, N, M	Alopecia; mucous condylomata lata	48	24	30	64	4	0	0	.....
9	21, W, F	Papular syphilid; condylomata lata	48	24	8	64	0	0	0	.....
10	20, N, M	Chancre	48	24	10	0	0	0	0	.....
11	24, N, F	Condylomata lata	18	72	12	64	No follow-up	0	0	.....
12	7, N, M	Papular syphilid	48	..	14	64	Patient still under observation	0	0	.....
13	20, N, M	Chancre	48	24	12	32	Patient still under observation	..	0	.....
14	20, N, M	Chancre	48	24	14	32	Patient still under observation	..	0	.....

administration of the drug was carefully supervised, and each dose was taken in the presence of a physician or nurse. Dark field examinations were performed at 12 to 24 hour intervals by a trained staff physician, and each specimen reported as giving negative results was examined by one of us. A serologic test for syphilis was made before treatment was given, and after the completion of therapy tests were repeated at weekly intervals for three months and after this at monthly intervals. A spinal fluid examination was made six months after the completion of treatment.

There were five Negro females, five Negro males, two white males and two white females in the series. The females ranged in age from 17 to 27, and the males from 7 to 55. Six patients had seropositive primary syphilis; two had seronegative primary syphilis, and six had secondary mucocutaneous lesions.

The schedule of treatment which we finally decided on as apparently effective consisted in an initial dose of 3 Gm. of chloramphenicol, followed by 0.5 Gm. every four hours to a total of 48 Gm. (15 days). Prior to our arrival at this schedule three patients were treated with other dosage schedules: one received a single dose of 3 Gm.; one received a 3 Gm. dose daily for five days, and one received a 3 Gm. dose daily for six days.

Results of Treatments with Chloramphenicol.—The patient treated with a single dose of 3 Gm. received it on June 27, 1949 and was still under observation at the time of writing. Forty-eight hours after administration of the drug the results on dark field examination were negative, and 11 days later the lesion was healed. The original titer was 16 units, and six months later it was negative. The results of spinal fluid examination were negative to the time of writing, and there had been no evidence of a clinical relapse.

The patient treated with a 3 Gm. dose daily for five days was dark field negative 24 hours after institution of treatment, and six days later all lesions had healed. This patient became pregnant and was re-treated with chloramphenicol although the titer had dropped from 64 to 4. She had a serorelapse after delivery of a normal child six months after treatment, and her titer rose to 64. The patient who received 3 Gm. daily for six days was the first one treated in this series. The dark field examination gave negative observations 72 hours after administration of the first dose of the drug, and in 12 days all the lesions were healed. Because the patient was pregnant, treatment with chloramphenicol was discontinued and a course of penicillin was given.

The remaining 11 patients received an initial dose of 3 Gm. followed with 0.5 Gm. every four hours to a total of 48 Gm. Results of dark field examinations were negative in 24 hours in all but one of these cases, and in this one they became negative in 48 hours. Rapid healing of all lesions was noted. All but one of these patients were still under observation at the time of writing. The exception had concomitant pulmonary tuberculosis, and after therapy with chloramphenicol for early syphilis she was transferred to a state sanatorium. The director of the sanatorium sent blood specimens for serologic tests at monthly intervals to our laboratory. The dark field observations on this patient were negative 24 hours after treatment was begun, and all lesions were healed within five days. The serologic titer on admission was 64 units; six months after completion of treatment, it was negative and the results of spinal fluid examination were also negative. Two of the men with chancres were seronegative at the start of treatment and remained so. One young Negro girl had condylomata lata at the time of the first visit and was also 7½ months pregnant. Chloramphenicol was the only antisyphilitic drug administered to this patient during her pregnancy. She was delivered of a full term

child who, studied carefully with x-ray examinations and serologic tests and clinically, was found to be nonsyphilitic. Three patients had not completed the preliminary follow-up period at this writing.

AUREOMYCIN

Reports of Previous Investigations.—O'Leary and his co-workers [4] were the first to report that aureomycin had antispirochetal activity when administered by mouth. Irgang and Alexander,[10] using different treatment schedules, treated nine patients who had early syphilis, eight of whom had dark field-positive lesions. The lesions remained dark field-positive from two to five days. Wiggall and his associates [5] treated 25 patients having dark field-positive lesions of early syphilis with various treatment schedules. They reported that the dark field observations became negative in about 72 hours, and in two of their patients the lesions healed in six days. At the time of their report the serologic reaction in three patients had undergone reversal to negative. Nelson [11] stated that this drug possesses a thousandth of the in vitro activity of crystalline penicillin G.

In order to complete our study on the effect of currently used antibiotic drugs in the treatment of syphilis and to determine whether or not aureomycin administered by the intravenous route was as effective as by the oral route, we treated 20 patients, 10 orally and 10 intravenously.

Method of Study.—The method of study with regard to aureomycin was as follows:

Observations were made on 20 patients with dark field-positive lesions of early syphilis who were treated with aureomycin either by mouth or by the intravenous method. Of the group treated orally, seven were admitted to the hospital so that the study could be more carefully controlled and so that dark field examinations could be carried out at regular intervals. Ten patients were treated in the outpatient department of the University of Maryland Hospital with daily intravenous injections of aureomycin, two treatment schedules being used. Three patients were treated as outpatients with aureomycin administered orally. The administration of the drug was always carefully supervised by a physician or nurse, except in those instances in which the patient was taking oral medication at home, presumably following the schedule as ordered.

There were six Negro males, three white males, nine Negro females and two white females in this series. The females ranged in age from 15 to 49, and the males from 17 to 37. Nine patients had chancres, and 11 had secondary mucocutaneous syphilis.

The following dosage schedules were used: (1) 100 mg. of aureomycin administered intravenously once daily for 15 days; (2) 200 mg. of aureomycin given intravenously once daily for 15 days; (3) 1 Gm. of aureomycin taken by mouth followed by two oral doses of 0.5 Gm. at four hour intervals (this dosage continued daily for 15 days; two patients treated on this schedule as outpatients), and (4) 3 Gm. at a single oral dose followed by 0.5 Gm. taken orally every four hours for 15 days (all patients treated on this schedule hospitalized, except one).

Results of Oral Treatment (tables 4 and 5).—Ten patients were treated by the oral route with two different schedules. The first two patients received 1 Gm. (4 capsules) followed by two doses of 0.5 Gm. (2 capsules) four hours apart, and this schedule was continued daily for 15 days. In both of these patients, the dark field

10. Irgang, S., and Alexander, E. R.: Treatment of Early Syphilis with Aureomycin, Harlem Hosp. Bull. **1**:91 (Dec.) 1948.

11. Nelson, R.: Personal communication to the authors

observations were negative 24 hours after the beginning of the treatment and the lesions were healed in seven days. Six months after the completion of therapy both patients had become seronegative and had negative results on spinal fluid examinations.

The remaining eight patients were given an initial dose of 3 Gm., and this was followed by 0.5 Gm. every four hours for 15 days. For ease of study, all these patients were admitted to the hospital and the administration of the drug was supervised by a physician and a nurse. The dark field observations became nega-

TABLE 5.—*Data on Treatment of Early Syphilis by Aureomycin Given Orally**

Case No.	Patient's Age, Race, Sex	Manifestation	Time Before Negative Dark Field Observations, Hours	Time for Healing of Lesions, Days	Serologic Titer on Admission	Titer After 6 Mo.	Cerebrospinal Fluid Reaction	Reactions to Aureomycin	Total Dose, Gm.
1	49, W, F	Papular syphilid; condylomata lata	24	7	32	0	0	Nausea	30
2	21, W, F	Chancre	24	7	8	0	0	Severe nausea and loss of appetite	30
3	32, N, F	Multiple chancres	24	10	16	Patient still under observation	..	Nausea and vomiting	48
4	19, N, M	Chancre	72	7	0	0	0	.....	48
5	18, N, F	Condylomata lata	48	12	32	Patient still under observation	..	.....	48
6	37, W, M	Chancre	24	7	4	Patient still under observation	..	.....	48
7	15, N, F	Condylomata lata	18	7	4	Patient still under observation	..	.....	48
8	27, W, M	Chancre	24	7	16	Patient still under observation	..	.....	48
9	19, N, M	Chancre	24	7	0	Patient still under observation	..	.....	48
10	18, N, F	Condylomata lata	48	12	64	Patient still under observation	..	.....	48

* Dosage schedules were as follows: in cases 1 and 2, 1 Gm., followed by two doses of 0.5 Gm., daily for 15 days, and in the other cases, 3 Gm., followed by 0.5 Gm. every four hours for 15 days.

tive from 18 to 72 hours after the initial dose was administered. The lesions in these patients healed in from seven to 12 days. Seven of these patients were still in the first six months observation period at the time of writing, but the three who completed the first period of observation had become seronegative and had negative results on spinal fluid examination. One of these, in whom the interval since treatment had been only three months, had a negative serologic reaction.

Results of Treatment by the Intravenous Method (table 6).—Ten patients were given daily intravenous injections of aureomycin hydrochloride with sodium glycinate for 15 days, six of them receiving 100 mg. daily, and the remaining four, 200 mg. a day. In all of these the dark field observations became negative in 24 to 48 hours. The lesions healed in seven to 14 days, 100 or 200 mg. being apparently

equally effective. Three of the patients became seronegative and had negative spinal fluid observations at the end of six months; three showed a drop in serologic titer, and four had not completed the preliminary six month observation period at this writing.

Reactions.—No adverse reactions were noted in the group of patients treated by the intravenous route, but two of the patients treated by the oral route had severe nausea and vomiting, and two had nausea only. Those treated with recrystallized aureomycin had not had any reactions to date.

TABLE 6.—*Data on Treatment of Early Syphilis with Aureomycin Given Intravenously*

Case No.	Patient's Age, Race, Sex	Manifestation	Dosage Schedule	Time Before Negative Dark Field Observations, Hours	Time for Healing of Lesions, Days	Serologic Titer on Admission	Titer After 6 Mo.	Cerebrospinal Fluid Reaction	Reactions to Aureomycin
1	18, N, F	Condylomata lata	100 mg. daily for 15 days	48	14	32	4	0	None
2	17, N, M	Condylomata lata	100 mg. daily for 15 days	48	14	64	Patient lost from observation		None
3	21, N, M	Chancre	100 mg. daily for 15 days	24	8	0	0	0	None
4	19, N, F	Chancre	100 mg. daily for 15 days	48	14	64	4	Patient still under observation	None
5	23, N, F	Condylomata lata	100 mg. daily for 15 days	24	10	64	4	Patient still under observation	None
6	36, W, M	Chancre	100 mg. daily for 15 days	24	10	8	0	0	None
7	28, N, M	Condylomata lata	200 mg. daily for 15 days	24	7	32	0	0	None
8	29, N, M	Condylomata lata	200 mg. daily for 15 days	48	14	16	Patient still under observation		None
9	21, N, F	Condylomata lata	200 mg. daily for 15 days	48	12	32	Patient still under observation		None
10	18, N, F	Condylomata lata	200 mg. daily for 15 days	48	7	32	Patient lost from observation		None

TERRAMYCIN

Previous Investigation.—At the time of this report there had been only one publication [12] on the effect of terramycin on T. pallidum.

Present Study.—Although the supply was limited, we felt that an evaluation of this drug was advisable to complete this study on the effect of the antibiotics in syphilis.

For the present report five patients were studied: two Negro males and three Negro females were hospitalized with dark field-positive lesions. One female was 3 years old.

12. Hendricks, F. D.; Greaver, A. B.; Olansky, S.; Taggart, S. R.; Lewis, C. N.; Landman, G. S.; MacDonald, G. R., and Welch, H.: Terramycin in the Treatment of Venereal Disease, J. A. M. A. **143**:4 (May 6) 1950.

An initial dose of 3 Gm. of terramycin followed by 0.5 Gm. every four hours for 15 days was the dosage schedule used. Thus, the same dosage schedule was used with terramycin that had been effective with chloramphenicol and aureomycin.

Results of Treatment.—The dark field observations were negative in 24 hours after the institution of therapy in four cases and in 32 hours in the fifth one. The moist genital lesions were completely healed in from seven to 12 days. There were no adverse reactions to the drug. The patients were discharged from the hospital after 15 days of therapy and reported to the outpatient department for follow-up. One was seronegative at the first visit and remained so. None of the patients had completed the preliminary six months follow-up at the time of writing.

SUMMARY

The first part of this study is devoted to penicillin and its effect on 127 patients treated by several different methods. Carinamide was administered concurrently to 27 patients treated with buffered penicillin tablets and penicillin in oil and wax, and, from our results, we are convinced that this drug did not enhance the value of penicillin; therefore, its use was discontinued. Of the group who were scheduled to be treated once weekly for 35 weeks with penicillin in oil and wax or procaine penicillin G in oil, only eight, or 18.6 per cent, completed the course; seven of those, however, who did not receive the entire course became seronegative and had negative results on spinal fluid examinations at the end of six months. Of the entire group of persons with uncomplicated early syphilis started on treatment 32.5 per cent obtained a satisfactory result in that the results of blood and spinal fluid examinations were negative six months after the completion of treatment. The group treated with penicillin tablets were given the medication on an outpatient status daily for 15 days. There were no adverse reactions in this group, but only 15.3 per cent completed the required amount of treatment, and of these none achieved a satisfactory result.

In the group of patients who had syphilis complicated by pregnancy, the attendance was regular and treatment was administered daily for 15 days, and, of these, 29 were hospitalized for the duration of treatment. There was only one case which could really be classed as showing a treatment failure in the group treated with procaine penicillin in oil; in it the patient received her treatment during the seventh month of pregnancy and the child had x-ray evidence of congenital syphilis. In the other showing "failure" the patient received only a single dose of 300,000 units of procaine penicillin in oil 24 hours before she was delivered of a stillborn child. In the group of women treated with penicillin in oil and wax there were four failures; one of these so-called failures, however, occurred in a woman who had a stillbirth after the fourth treatment. Of the women treated with penicillin tablets 33.5 per cent were delivered of congenital syphilitic children. All these women had been hospitalized for the duration of treatment.

Chloramphenicol was administered to 14 patients with dark field-positive lesions of early syphilis, and in eight of them (71.4 per cent) the dark field observations became negative in 24 hours; in the rest they became negative in from 48 to 72 hours. Ten of these patients completed the preliminary six months follow-up period, and, of these, seven (70 per cent) became seronegative and had negative results on spinal fluid examinations; two showed a drop in serologic titer from 64

to 4. Two pregnant women were treated with chloramphenicol, and both of them were delivered of normal nonsyphilitic infants.

Aureomycin was administered to a total of 20 patients, 10 of them receiving the drug by mouth and 10 receiving it by the intravenous route. With the oral treatment the dark field observations became negative in from 18 to 72 hours. The lesions healed in seven to 12 days in all the cases. Three of the patients completed the preliminary six month observation period and became seronegative and had negative spinal fluid reactions; the remaining seven were still in the first observation period at the time of writing. Of the 10 patients who were treated by the intravenous route two had not completed the preliminary six month follow-up period. Two patients completed the course of treatment but were lost from observation. Three became seronegative and had negative results of spinal fluid examinations, and three showed a decided drop in the serologic titer. The lesions in this group healed in from seven to 14 days whether the patients received 100 or 200 mg. daily.

The five patients treated with terramycin had negative dark field observations 24 to 32 hours after the institution of treatment. The lesions healed in from seven to 12 days. One patient who was seronegative at the time of admission remained so to the time of this report.

CONCLUSIONS

Any system of syphilotherapy which advocates administration of medication by the oral route requires hospitalization of the patient for careful supervision by trained personnel.

The administration of penicillin in the form of buffered tablets in the dosage used by us is an unsatisfactory method of treatment for syphilis.

Only 18.6 per cent of 43 patients returned regularly at weekly intervals for the 35 week course of penicillin injections, this observation proving that the majority of patients will not return at weekly intervals over a long period regardless of whether or not the medication administered is free.

Among those patients who completed the course of weekly treatments the percentage of satisfactory results was high.

The results obtained in this study indicate that the concurrent administration of carinamide with penicillin is of no value in the treatment of syphilis.

Chloramphenicol appeared to be an effective agent in the treatment of early syphilis in this group of cases. Rapid healing of lesions was noted, and reversal of the serologic reaction to negative was observed in 70 per cent of the cases.

It is obvious that more investigative work, with longer follow-up, must be carried out with chloramphenicol.

Aureomycin administered by the intravenous or by the oral route will cause a disappearance of surface T. pallidum in 18 to 72 hours.

Aureomycin administered by either route will cause the lesions of early syphilis to heal in seven to 14 days. Aureomycin will produce a reduction in serologic titer, as demonstrated in those patients with early syphilis who completed the preliminary observation period. Further studies must be carried out to determine an optimum dose.

No reactions to penicillin or chloramphenicol were encountered in this series, but several patients treated with aureomycin complained of nausea and vomiting or

severe nausea and loss of appetite. In those treated with recrystallized aureomycin there were no reactions.

Two pregnant patients with early syphilis treated with chloramphenicol were delivered of nonsyphilitic infants.

In the five cases in which its effect was studied, terramycin caused surface T. pallidum to disappear in from 24 to 32 hours and lesions to heal in seven to eight days.

Further studies must be carried out on terramycin to determine its value in syphilotherapy.

ABSTRACT OF DISCUSSION

Dr. William B. Guy, Pittsburgh: First I wish to pay my respects to the authors for a thorough, exhaustive piece of work. This sort of clinical research is time consuming and often exasperating, particularly where repeated dark field examinations must be made or tracking down patients for serologic and clinical follow-ups is necessary.

Especially does that situation exist now, when the large urban centers, once the great reservoirs for early syphilitic infection and hence fertile fields for evaluation of new treatment schedules and new drugs, have such a lowered incidence of early syphilis. This lowered incidence is due largely to the vast syphilis control programs which are operating in most cities and to the relative ease and safety of rapid treatment schedules with penicillin.

In Pittsburgh, for instance, in 1946 there were 721 cases of primary and secondary syphilis reported to the Pittsburgh syphilis control program, in 1948 there were 493, and for the first five months of 1950, only 29. At present it takes a long time to assemble a large enough number of persons with early infections to evaluate thoroughly a new drug or treatment schedule. The authors report 29 patients treated with aureomycin, chloramphenicol and terramycin—hardly a respectable figure for study of a new drug 10 years ago, but in 1950 a sizable collection.

As regards their results with penicillin, I have only two comments to make. The failure to hold the majority of patients given a 35 week course with weekly injections shows the great advantage from a public health standpoint of safe, relatively comfortable rapid treatment. If patients now lose interest in weekly injections of penicillin, we wonder how many balked and quit in days of arsphenamine, neoarsphenamine or even oxophenarsine hydrochloride (mapharsen®). The results in the series of cases complicated by pregnancy were similar to those found by other investigators and ourselves. At Elizabeth Steel Magee Hospital in Pittsburgh we developed a schedule for pregnant women with late latent syphilis or women who were gravid and had had previous treatment, most of whom had had arsenicals given weekly during many previous pregnancies. We gave 600,000 units of procaine penicillin in oil with aluminum monostearate twice weekly for six injections. Results were quite satisfactory as far as the infants were concerned, and so we decided to use this schedule in treatment of some early infections in pregnancy. To date we can report on three pregnant women with early latent syphilis so treated and one gravid female with secondary syphilis so treated who, with their infants, have been clinically and serologically followed for six months. In every instance the serologic reaction either reverted to negative or continued to fall in titer, and there was no evidence of clinical activity of the disease in the babies or mothers.

It would appear that both chloramphenicol and aureomycin are going to prove to be effective antisyphilitic drugs. The single case of the authors that stands out in my mind is that of the patient who received a single dose of 3 Gm. of chloramphenicol: "Forty-eight hours after the administration of the drug the results on dark field examination were negative, and 11 days later the lesion was healed. The original titer was 16 units, and six months later it was negative. The results of spinal fluid examination were negative to the time of writing, and there had been no evidence of a clinical relapse."

Are we on the verge of Ehrlich's dream of therapia sterilisans magna? If this trend continues, syphilotherapy will be in the hands of pharmacists.

I think that from now on evaluation of antisyphilitic drugs will be a lengthy, tedious procedure, barring war or national disaster. If the incidence of early syphilis continues to decline, it will take a long time to collect a series of cases that is statistically significant.

Large clinics and treatment centers will again be expending their main efforts on late syphilis. Such cases will inevitably appear from the ranks of those who escaped treatment for early syphilis, who were inadequately treated or who were inadequately followed up. In these cases evaluation of treatment takes years of observation. The shift in emphasis will be welcome to most avid syphilologists. The change of interest from mass treatment programs to management of individual cases will mean too that the "old syphilitic" will again come into his own.

DR. A. B. LOVEMAN, Louisville, Ky.: I think we should compliment and thank Dr. Robinson not only for the caliber of his paper but also for reminding us, as dermatologists, that we are also syphilologists.

Dr. William Buschemeyer of Louisville, Dr. Fred Zuagg, who is now associated with Dr. Curtis in Ann Arbor, and I have undertaken a study in which we are giving 300,000 units of penicillin G with aluminum monostearate at weekly intervals for four successive weeks. We have followed over 80 per cent of the cases for more than six months, and about 60 per cent for more than a year. Our results, to date, have been clinical cures in slightly over 90 per cent of the cases.

The over-all percentage of cures, including serologic cures, has been approximately 85 per cent. We do not advocate the schedule outlined as a method of treating early syphilis, but we wanted to have our results compared with the excellent results of Dr. Robinson.

DR. DUDLEY SMITH,† Charlottesville, Va.: Those of us who have been dealing with the spirochete for a number of years undoubtedly have more regard for some of the difficulties associated with it than have some of the younger persons in public health work at the present. There is no doubt, however, that the introduction of penicillin and some of the newer antibiotics in the management of syphilis is the greatest stride that has been made in the history of medicine. We have not yet reached the stage, though, where we can say that with penicillin given over a relatively short period we are going to get cures in 100 per cent of the cases. Even with the moderately long schedules that have been used experimentally by us for eight or 10 years now, there is still an incidence of failures of 10 to 15 per cent.

I feel certain in my own mind that much of the publicity given not only in the field of syphilology but also in the field of psychiatry and neurology may lead to a certain amount of harm. Too much emphasis has been placed on the fact that syphilis can be cured in from five to 15 days. My opinion is based, as I said, on past clinical experience, and also I think, the contention has been cleared up to a certain extent by more recent advances in experimental work. Some of you have already heard in papers read here or seen in published articles something about the studies that have been made on T. pallidum in the various short stages, and so forth, and the observations made probably explain some of the poor results of treatment. On that basis, it seems to me that the practical thing for us to do would be to give treatment over a longer period to patients with syphilis. I am not sure that there is much necessity for adding any agent other than the antibiotics, and particularly penicillin. Still, some people do feel that bismuth, and maybe arsenic, should be retained for certain cases.

There is another very important item, it seems to me, in regard to the management of syphilis at the present. The agents that we have available now are very different from those used at first. When we first began experimental work in the treatment of early syphilis—or of any stage of syphilis, for that matter—people were hospitalized and given injections every two to three hours around the clock. Now that the vehicle that contains the material has been altered to the point where injections can be given at infrequent intervals, so that treatment can easily be carried over a longer period, we are giving our patients 1,200,000 units of penicillin in oil and aluminum monostearate once a week for five to 10 weeks. This method does not cause any discomfort. The injection is proved to cause an effective blood level over a period of from six to 10 days.

DR. NORMAN EPSTEIN, San Francisco: I should like to compliment the Robinsons for their studies of new antisyphilitic remedies. I think there has been a tendency to regard penicillin as the complete answer to the problem of syphilotherapy. As Dr. Smith has said, this drug certainly has revolutionized antisyphilitic treatment, but is it the whole answer?

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† Dr. Smith died on Aug. 30, 1950.

In a recent paper Chargin pointed out that after therapy with penicillin syphilis acts exactly as it did on treatment with arsphenamine and bismuth. If you search the literature and analyze it carefully, you will find, he says, that seronegative primary syphilis is curable in practically 100 per cent of the cases. In seropositive primary syphilis the percentage of cure drops to 92 per cent. In secondary syphilis it drops to 75 per cent, and in the early latent stage, to 60 or 55 per cent. Syphilis responded in about the same way under other types of therapeutic attack. Further, a review and analysis of the literature would seem to point to the fact that our results with penicillin therapy in late latent and late syphilis may not be as good as we hoped, that one course of penicillin may not protect the patient from future development of lesions. Therefore, the search for other antisyphilitic agents is very important, and this work should be continued.

I should like to comment about the decreasing incidence of syphilis, especially acute syphilis. It is an amazing thing that has happened throughout this country and in other parts of the world. Syphilologists of considerable experience hesitate to attempt to explain this decrease. Is it due to penicillin? Is it due to our public health measures? In discussing this problem, syphilologists hesitate to accept these explanations because similar events have occurred in the history of this disease before. I should like to report that at the Marine Hospital of this city, where most of the cases of acute syphilitic infections encountered were contracted in the Orient, the decrease has been just the same. In the years 1946 and 1947, the approximate number of cases of primary and secondary syphilis seen there was from 200 to 250. For the first quarter of this year, there were 20, a decrease of approximately 60-odd per cent. These facts have to be studied carefully before we assume that penicillin therapy alone is responsible for the lessened incidence of the disease.

DR. HARRY ROBINSON SR., Baltimore: I thank the discussers, and I shall try to answer them.

Dr. Epstein and Dr. Guy mentioned the lower incidence of syphilis. This is easily explained. It isn't due to the antibiotics. During and after each war there is a high incidence of syphilis. For a few years after the last war that continued, and then syphilis found its level. In 1945, 1946 and 1947 we had a very high incidence of syphilis, and the present incidence is just normal, for our community, at least. We don't believe it is due in any way to treatment.

Dr. Guy wondered how many had failed to go through treatment under the old regimen. In Baltimore, only 10 per cent of the patients ever followed through a complete course of arsenic and bismuth therapy. Although treatment is free to patients, they will not go through a long course of therapy, although we cut our course down to 35 weeks.

Everyone is trying to accomplish a quick cure. Several investigators, notably in New York, have tried to produce a cure by one injection. A discusser at a meeting of the American Venereal Disease Association reported on a group in which some patients received one injection of 1,200,000 units; other patients, 2,400,000 units in two injections, and then others, three injections of 1,200,000 units. I question whether these large injections will cure the disease any more effectively than 300,000 units a day.

Dr. Guy needn't worry about the druggist's role in therapy because antibiotics should be given by injections.

I do not suggest that procaine penicillin in oil is the drug of choice. Aqueous procaine penicillin gives as good a result. I don't know whether it is the blood level or something inherent in the drug itself that is the important factor.

Dr. D. C. Smith mentioned the harm caused in the minds of the laity by our advising short time treatment. It certainly is advisable to get a larger number of patients who will take a short course of treatment than a smaller number who will take a long course of treatment. When you compare the results of those two schedules, the percentage of so-called cures is seen to be much greater in the short period treatments.

In answer to Dr. Epstein, no one knows whether or not the final answer to the question of syphilotherapy is in penicillin. The finding of a drug which will avoid the serious reactions obtained from arsenicals and give a cure in a short space of time is a desirable goal. Whether penicillin is that drug, we don't know. We worked with the other drugs because a good many patients have reactions to penicillin. In cases in which they do and it is desirable to continue treatment, we change to aureomycin or terramycin.

PLASMA PROTEINS IN VARIOUS DISEASES OF THE SKIN

Electrophoretic Studies

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HUMAN blood plasma contains a complex mixture of proteins.[1] Only since the introduction of electrophoretic analysis by Tiselius,[2] has a thorough and reliable study of the plasma proteins been possible. Before then the only practical method had been the determination of albumin and globulin by the salting-out method of Howe,[3] which, in comparison with electrophoretic analysis, is crude and often misleading. Several reviews of the data obtained in various diseases by electrophoretic analysis of the blood plasma have been published in recent years,[4] but the number of determinations in dermatologic conditions is still small.

In this communication the electrophoretic data obtained by us in various dermatologic conditions will be presented and compared with the results reported by other authors. In many instances the data obtained with the Howe method by previous authors and by ourselves will also be given, in order to afford an opportunity for one to compare these values with the electrophoretic values.

The great discrepancy that often exists between the values obtained by electrophoresis and those secured by the Howe method as well as the reasons for this discrepancy have been discussed in detail in a previous communication.[5] It was

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From the Department of Dermatology, Harvard Medical School, and the Dermatologic Service, Massachusetts General Hospital.

1. Lever, W. F.; Gurd, F. R. N.; Uroma, E.; Brown, R. K.; Barnes, B. A.; Schmid, K., and Schultz, E. L.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XL. Quantitative Separation and Determination of the Protein Components in Small Amounts of Normal Human Plasma, J. Clin. Invest. **30**:99, 1951.

2. Tiselius, A.: A New Apparatus for Electrophoretic Analysis of Colloidal Mixtures, Tr. Faraday Soc. **33**:524, 1937.

3. Howe, P. E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood, J. Biol. Chem. **49**:93, 1921.

4. Stern, K. G., and Reiner, M.: Electrophoresis in Medicine, Yale J. Biol. & Med. **19**:67, 1946. Luetscher, J. A., Jr.: Biological and Medical Applications of Electrophoresis, Physiol. Rev. **27**:621, 1947. Gutman, A. B.: The Plasma Proteins in Disease, in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, Inc., 1948, vol. 4, p. 155.

5. Lever, W. F.: The Proteins in Pemphigus Vulgaris: I. Electrophoretic Analysis of the Proteins in the Blood Serum of Patients with Pemphigus Vulgaris, J. Invest. Dermat. **14**: 205, 1950.

pointed out that the "albumin" fraction obtained by the Howe method contains not only the albumin but also most of the alpha globulins which are thus counted as albumin. In normal blood serum, in which the alpha globulins amount to only 15 per cent of the total protein, the discrepancy between the electrophoretic albumin value and the value of the Howe albumin fraction is fairly small. However, in those diseases in which the albumin is decreased and the alpha globulins are increased the discrepancy is considerable because, with the Howe method of albumin determination, the decrease in albumin is masked to a considerable degree by the increase in the alpha globulins. The Howe albumin value may then exceed the correct value of albumin, as obtained by electrophoresis, by 100 and even 150 per cent. On the other hand, the Howe method serves as a good indicator for an increase in the amount of gamma globulin. Since the Howe globulin fraction consists almost entirely of the beta and gamma globulins and the beta globulins show significant changes of their nitrogen content in very few diseases, an increase in the Howe globulin fraction can, as a rule, be interpreted as an increase in the gamma globulin.

METHODS

The concentration of total protein in the blood serum or in heparinized blood plasma was determined by the micro-Kjeldahl method with the use of a nitrogen factor of 6.25.

Electrophoretic analyses were carried out in the Tiselius apparatus on either serum or plasma as described in a previous communication.[5] Sodium diethylbarbiturate (barbital sodium U. S. P.) at pH 8.6 and ionic strength of 0.1 was used as buffer.

For the determination of the "albumin" and "globulin" fractions with the Howe method[8] the "globulin" fraction of the blood serum was salted out, i. e., precipitated, with 22.2 per cent sodium sulfate. The amount of protein in the filtrate was determined and regarded as the "albumin" fraction. The difference between the amounts of total protein and protein in the "albumin" fraction was taken as the value of the "globulin" fraction.

RESULTS OF ELECTROPHORETIC ANALYSES IN INFLAMMATORY DISEASES

Eczema.—Review of Literature: Robert[6] reported electrophoretic data on two cases of extensive erythroderma, one caused by sensitivity to arsphenamine and the other by sensitivity to mercury. Both patients showed pronounced hypoproteinemia (4.7 and 4.9 Gm. per 100 ml. of serum, respectively) and reduced values for albumin (41.1 and 37.6 per cent, respectively). The first patient, who was in poor condition, had moderately increased values for alpha-1 and alpha-2 globulins (9.1 and 17.5 per cent), while the second patient, who was in good general condition, showed normal values for the alpha globulins but a marked increase in the gamma globulin, to 33.2 per cent.

Determination of the total protein and of the albumin and globulin fractions with the Howe method in eczema revealed normal values in cases of limited extent.[7] In patients with fairly extensive involvement, particularly when accom-

6. Robert, P.: Serumuntersuchungen, insbesondere mit der Elektrophorese, bei veschiedenen Hautkrankheiten, Dermatologica (supp.) **97**:89, 1948.

7. (*a*) Cerutti, P.: Le frazioni proteiche del siero nelle malattie cutanee e nella sifilide, Gior. ital. dermat. e sif. **73**:858, 1932. (*b*) Midana, A.: L'equilibrio proteico del sangue in alcune dermatosi, Dermosifilografo **8**:173, 1933. (*c*) Mulvehill, W.: Serum Protein in Dermatoses, Arch. Dermat. & Syph. **49**:327 (May) 1944.

TABLE 1.—*Electrophoretic Data on Patients with Various Dermatoses*

No. of Patient	Total Protein (Nitrogen Factor, 6.25), Gm./100 Ml.	Howe Values, Gm./100 Ml.		Relative Electrophoretic Concentrations, Per Cent of Total Protein						Absolute Electrophoretic Concentrations, Gm./100 Ml.						Duration	Comments
		Albumin	Globulin	Albumin	α-1	α-2	β-1	β-2	γ	Albumin	α-1	α-2	β-1	β-2	γ		
Normal Values																	
	6.80	4.50	2.30	55.0	5.0	10.0	15.0	4.0	11.0	3.74	0.34	0.68	1.02	0.27	0.75	.....	Serum
	7.10*	....	....	53.0	5.0	10.0	14.0	8.0*	10.0	3.76	0.36	0.71	0.99	0.57*	0.71	.....	Plasma
Eczema																	
1	7.38	3.48	3.90	35.2	7.6	9.4	23.1	4.2	20.5	2.60	0.56	0.69	1.70	0.31	1.51	7 yr.	Seborrheic dermatitis, extensive
2	7.11*	....	....	41.7	7.6	11.1	13.0	10.1*	16.6	2.96	0.54	0.79	0.92	0.72*	1.18	4 mo.	Seborrheic dermatitis, extensive
3	7.43	....	....	47.7	5.8	9.4	14.8	4.5	17.9	3.54	0.44	0.70	1.10	0.33	1.33	13 yr.	Atopic eczema, extensive
4	6.96	....	....	59.9	5.2	10.4	12.5	3.8	8.3	4.17	0.36	0.72	0.87	0.26	0.58	22 yr.	Atopic eczema, localized
5	5.32	3.05	2.27	43.5	10.8	10.1	17.3	4.5	13.8	2.31	0.57	0.54	0.92	0.24	0.73	3 mo.	Dermatitis due to gold, extensive
6	6.42	2.32	4.10	31.1	6.8	9.0	12.5	5.9	34.7	1.99	0.44	0.58	0.81	0.38	2.23	3 yr.	Generalized exfoliative dermatitis
7	6.40	3.30	3.10	48.6	7.5	10.9	6.5	5.6	21.0	3.11	0.48	0.70	0.42	0.35	1.34	3 mo.	Generalized exfoliative dermatitis
8	6.40	3.29	3.11	41.5	9.9	12.7	14.8	4.5	16.8	2.66	0.63	0.81	0.95	0.29	1.08	2 yr.	Generalized exfoliative dermatitis
Psoriasis																	
1	7.15*	4.32	2.63	48.8	6.9	10.1	17.3	8.3*	8.7	3.49	0.49	0.72	1.24	0.59*	0.62	11 yr.	Extensive discoid
2	6.24	3.90	2.34	41.3	11.8	11.0	16.6	7.2	12.1	2.58	0.74	0.69	1.04	0.45	0.76	40 yr.	Generalized erythroderma, 4 wk.
3	6.05	4.24	1.81	55.4	8.5	12.6	14.7	2.2	6.6	3.35	0.51	0.76	0.89	0.13	0.40	18 yr.	Generalized erythroderma, 1 wk.
4	6.88	....	....	54.7	6.5	15.8	14.1	1.8	7.1	3.76	0.45	1.10	0.97	0.12	0.49	.....	Generalized erythroderma; rheumatoid arthritis
5	6.45*	4.18	1.90	45.5	8.0	14.1	13.5	10.6*	8.4	2.93	0.52	0.91	0.87	0.68*	0.54	25 yr.	Generalized erythroderma, 15 mo.; rheumatoid arthritis
..	6.20	....	....	45.6	11.7	14.9	14.1	3.7	10.0	2.83	0.73	0.92	0.87	0.23	0.62	.....	Generalized erythroderma, 17 mo.
..	6.06*	3.40	2.18	36.2	10.0	15.7	17.0	11.4*	9.7	2.19	0.61	0.95	1.03	0.69*	0.59	.....	Generalized erythroderma, 23 mo.
..	4.32	2.59	1.73	41.9	11.1	15.9	14.3	3.7	13.3	1.81	0.48	0.69	0.62	0.16	0.57	.....	Generalized erythroderma, 25 mo.
6	6.03	3.69	2.34	45.2	8.7	9.3	14.7	6.2	16.0	2.73	0.52	0.56	0.89	0.37	0.96	26 yr.	Generalized erythroderma, 1 mo
Pemphigus Foliaceus																	
1	4.60	2.35	2.25	38.8	10.8	11.8	14.6	4.9	19.6	1.78	0.50	0.54	0.67	0.23	0.90	14 mo.	.....
2	7.47*	....	....	48.1	8.8	9.9	10.4	10.8*	12.0	3.59	0.66	0.74	0.78	0.81*	0.90	4 mo.	.....
..	6.28*	3.31	1.75	38.6	9.6	12.1	12.2	12.9*	14.8	2.42	0.60	0.76	0.77	0.81*	0.93	6 mo.	.....
3	7.02	3.79	3.23	33.9	11.4	19.3	12.9	4.5	18.0	2.38	0.80	1.35	0.91	0.32	1.26	5 mo.	.....
..	5.82*	2.80	2.38	36.1	9.6	12.6	13.7	12.4*	15.8	2.10	0.56	0.73	0.80	0.72*	0.92	8 mo.	.....
..	5.56*	2.51	2.74	34.3	7.6	18.6	12.3	12.9*	14.5	1.91	0.42	1.03	0.68	0.72*	0.81	9 mo.	.....
4	7.20	4.34	2.86	39.3	7.3	16.0	12.1	4.7	20.5	2.83	0.53	1.15	0.87	0.34	1.47	32 yr.	.....

Pemphigus Vegetans																
1	7.69	5.40	2.29	51.6	5.4	9.9	14.9	3.4	14.8	3.97	0.42	0.76	1.15	0.26	1.14	1½ mo.	.....
..	6.10	....	....	41.6	9.9	10.6	17.3	4.5	16.1	2.54	0.61	0.65	1.06	0.27	0.98	2 mo.	.....
..	5.40	....	....	35.0	14.7	17.0	11.1	2.6	19.5	1.89	0.79	0.92	0.60	0.14	1.05	3 mo.	.....
2	6.04	3.14	2.90	40.7	8.3	10.8	14.3	2.6	23.3	2.46	0.50	0.65	0.86	0.16	1.41	19 mo.	.....
..	6.10	....	....	42.6	8.4	7.7	12.2	4.0	25.1	2.59	0.51	0.47	0.74	0.24	1.53	20 mo.	.....
..	6.90	4.15	2.75	57.0	5.8	5.0	5.8	2.0	24.5	3.93	0.40	0.35	0.40	0.14	1.69	21 mo.	.....
Erythema Multiforme																	
1	7.10	....	....	56.4	5.5	3.7	15.9	4.7	13.8	4.00	0.39	0.26	1.13	0.33	0.98	12 days	Blood serum; bullous type
..	5.10	....	....	58.2	8.7	9.0	8.6	4.8	10.7	2.97	0.44	0.46	0.44	0.24	0.55	.....	Blister fluid
2	7.50	4.24	3.26	54.1	4.9	9.9	12.8	3.8	14.4	4.06	0.37	0.74	0.96	0.29	1.08	6 days	Blood serum; bullous type
..	5.35	....	....	55.7	4.5	9.8	10.4	3.9	15.5	2.98	0.24	0.52	0.56	0.21	0.83	.....	Blister fluid
3	7.08	....	....	53.1	7.4	16.2	11.8	2.7	8.8	3.76	0.52	1.15	0.84	0.19	0.62	5 days	Blood serum; Stevens-Johnson type
4	5.00	....	....	34.2	11.8	13.6	12.4	8.1	19.9	1.71	0.59	0.68	0.62	0.41	1.00	1 wk.	Blood serum; due to phenolphthalein
..	3.40	....	....	42.4	14.1	12.6	9.0	8.3	13.6	1.44	0.48	0.43	0.31	0.28	0.46	.....	Blister fluid
Dermatitis Herpetiformis																	
1	7.22	....	....	62.8	5.8	8.7	12.4	2.5	7.9	4.53	0.42	0.63	0.90	0.18	0.57	8 yr.	.....
2	7.21	....	....	58.5	5.6	11.2	12.0	3.8	9.0	4.22	0.40	0.81	0.87	0.27	0.65	7 mo.	.....
3	6.28	....	....	50.2	6.3	9.8	19.0	3.9	11.0	3.15	0.40	0.62	1.19	0.24	0.69	8 yr.	.....
4	6.59	....	....	51.6	6.1	11.9	14.1	3.9	12.6	3.40	0.40	0.79	0.93	0.26	0.83	20 yr.	.....
5	6.59	....	....	58.3	6.8	8.2	14.2	3.5	9.2	3.84	0.45	0.54	0.94	0.23	0.60	18 mo.	.....
Erythema Nodosum																	
1	7.32	....	....	42.9	7.0	15.4	14.5	4.6	15.7	3.14	0.51	1.13	1.06	0.34	1.15	6 wk.	.....
Lupus Erythematosus																	
1	7.45	....	....	48.8	7.7	13.6	13.9	4.4	11.6	3.64	0.57	1.01	1.04	0.33	0.86	12 yr.	Chronic discoid
2	7.06	....	....	55.5	5.8	10.4	14.8	2.5	11.0	3.92	0.41	0.73	1.05	0.18	0.78	7 mo.	Chronic discoid
3	7.01	....	....	51.5	6.2	10.3	15.1	3.5	13.8	3.61	0.43	0.72	1.06	0.25	0.97	14 yr.	Chronic discoid, extensive
1	6.80*	3.94	2.46	49.2	5.5	10.0	14.8	6.4*	14.2	3.35	0.37	0.68	1.01	0.44*	0.97	10 mo.	Subacute disseminate
2	7.40*	....	....	45.6	7.5	11.2	10.6	7.7*	17.4	3.37	0.56	0.83	0.78	0.57*	1.29	8 mo.	Subacute disseminate
1	7.40	3.94	3.46	42.0	5.3	10.3	17.3	6.6	18.2	3.11	0.39	0.76	1.28	0.49	1.35	3 wk.	Acute systemic
..	4.95	2.38	2.57	34.5	7.7	8.0	14.4	7.9	27.4	1.71	0.38	0.40	0.71	0.39	1.36	7 wk.	Acute systemic
2	6.67	....	....	46.3	8.2	11.6	10.5	4.2	19.2	3.09	0.55	0.77	0.70	0.28	1.28	2 mo.	Acute systemic
3	5.00*	....	....	44.3	6.1	15.6	8.8	8.2*	17.0	2.22	0.31	0.78	0.44	0.41*	0.85	2 mo.	Acute systemic
4	8.00	3.40	4.60	44.6	5.7	6.9	10.4	4.1	28.2	3.57	0.46	0.55	0.83	0.33	2.26	2 mo.	Acute systemic, start of first course ACTH (5/19/49)
..	7.20	....	....	45.8	5.8	7.1	10.1	3.3	27.9	3.30	0.42	0.51	0.73	0.24	2.01	.....	Acute systemic, during first course ACTH (5/23/49)

* Determination includes fibrinogen.
† Determination of total protein by refractometry. The calculation of the absolute electrophoretic values in the patients with xanthomatosis is based on the refractometric values.

TABLE 1.—*Electrophoretic Data on Patients with Various Dermatoses—Continued*

No. of Patient	Total Protein (Nitrogen Factor, 6.25), Gm./100 Ml.	Howe Values, Gm./100 Ml.		Relative Electrophoretic Concentrations, Per Cent of Total Protein						Absolute Electrophoretic Concentrations, Gm./100 Ml.						Duration	Comments
		Albumin	Globulin	Albumin	α-1	α-2	β-1	β-2	γ	Albumin	α-1	α-2	β-1	β-2	γ		
										Lupus Erythematosus—Continued							
..	5.90	2.70	3.20	46.1	6.1	6.1	13.1	4.6	24.0	2.71	0.36	0.36	0.77	0.27	1.42	.....	Acute systemic, end of first course ACTH (5/31/49)
..	7.30	4.10	3.20	51.9	4.4	11.1	11.6	3.4	17.5	3.79	0.32	0.81	0.85	0.25	1.28	.....	Acute systemic, start of second course ACTH (6/22/49)
..	6.61	....	....	48.7	5.7	11.7	12.2	3.6	18.0	3.22	0.38	0.77	0.81	0.24	1.19	.....	Acute systemic, end of second course ACTH (6/30/49)
5	6.65	3.92	3.73	46.8	4.8	11.7	14.2	3.7	19.0	3.11	0.32	0.78	0.94	0.24	1.26	7 mo.	Acute systemic
..	6.70	3.36	3.34	34.7	6.5	11.1	14.8	3.4	29.4	2.32	0.44	0.74	0.99	0.23	1.97	9 mo.	Acute systemic
6	7.72	4.06	3.66	41.2	4.6	5.3	10.1	3.4	35.3	3.18	0.36	0.41	0.78	0.26	2.73	9 mo.	Acute systemic
7	7.86	3.64	4.22	33.9	8.0	11.1	11.3	2.9	32.7	2.66	0.63	0.87	0.89	0.23	2.57	2 yr.	Acute systemic
										Dermatomyositis							
1	4.10	2.28	1.82	28.9	19.0	25.9	8.9	5.2	12.1	1.18	0.78	1.06	0.36	0.21	0.50	4 wk.	Fulminating
2	6.53	4.26	2.27	46.4	7.5	13.7	13.4	6.0	12.9	3.03	0.49	0.89	0.88	0.39	0.84	3 mo.	.....
..	7.64*	4.60	2.28	52.2	5.9	15.2	9.1	6.2*	11.1	3.99	0.45	1.16	0.69	0.50*	0.85	22 mo.	.....
3	5.50	....	....	38.9	7.4	17.3	11.6	5.7	19.1	2.14	0.41	0.95	0.64	0.31	1.05	2 mo.	.....
..	6.44	....	....	42.4	4.6	12.7	17.6	4.5	18.2	2.73	0.30	0.82	1.13	0.29	1.18	6 mo.	.....
										Scleroderma							
1	6.54	....	....	61.6	5.7	11.8	11.8	1.7	7.4	4.02	0.37	0.77	0.77	0.11	0.48	1 yr.	Circumscribed, en bande
2	6.59	....	....	54.9	5.4	10.5	16.6	2.8	10.0	3.62	0.36	0.69	1.09	0.18	0.66	7 mo.	Circumscribed, small area
3	7.65	....	....	48.2	6.8	13.5	14.5	4.0	13.1	3.69	0.52	1.03	1.12	0.31	1.00	5 yr.	Circumscribed, extensive
1	5.92	....	....	54.3	6.6	10.1	15.0	1.5	12.6	3.21	0.39	0.60	0.88	0.09	0.75	2 yr.	Generalized, mild, before ACTH
..	5.12	....	....	54.9	7.6	10.6	17.4	2.6	6.8	2.81	0.39	0.54	0.89	0.13	0.35	.....	Generalized, mild, after 2 wk. of ACTH
2	6.80	4.20	2.60	51.9	6.8	14.1	14.7	3.6	9.0	3.52	0.46	0.96	1.00	0.24	0.61	3 yr.	Generalized, mild, before ACTH
..	6.30	....	....	56.5	5.0	11.3	17.9	2.9	6.5	3.50	0.32	0.71	1.13	0.18	0.41	.....	Generalized, mild, after 2 wk. of ACTH
3	6.00	....	....	44.9	10.3	17.4	11.9	1.5	14.0	2.69	0.62	1.04	0.71	0.09	0.84	3 yr.	Generalized, visceral, before ACTH
..	6.38	....	....	44.6	11.6	20.4	11.6	1.1	11.0	2.83	0.74	1.30	0.74	0.07	0.70	.....	Generalized, visceral, after 2 wk. of ACTH
4	7.30	....	....	38.4	7.4	10.4	13.2	5.4	25.2	2.76	0.53	0.75	0.95	0.39	1.81	4 yr.	Generalized, severe, before ACTH
..	6.40	....	....	48.0	4.1	14.2	13.0	3.7	17.1	3.07	0.26	0.91	0.83	0.24	1.09	.....	Generalized, severe, after 2 wk. of ACTH
5	6.80	....	....	40.3	8.2	10.5	14.1	4.2	22.8	2.74	0.56	0.71	0.96	0.29	1.55	6½ yr.	Generalized, severe
..	7.60	....	....	43.5	5.2	7.6	17.7	3.5	22.5	3.30	0.40	0.58	1.35	0.27	1.71	7½ yr.	Generalized, severe, before ACTH
..	6.50	....	....	48.3	7.1	7.6	15.5	3.8	17.6	3.14	0.46	0.49	1.01	0.25	1.14	.....	Generalized, severe, after 2 wk. of ACTH
6	8.38	4.08	4.30	44.7	4.6	6.8	10.8	5.6	27.4	3.75	0.39	0.57	0.91	0.47	2.30	2¼ yr.	Generalized, severe

7	7.00	....	....	40.9	7.8	13.2	13.7	4.2	20.2	2.86	0.55	0.92	0.96	0.29	1.41	5 yr.	Generalized, severe
8	8.66	....	....	38.8	6.4	11.0	7.5	2.3	34.2	3.36	0.55	0.95	0.65	0.20	2.96	10 yr.	Generalized, severe; calcinosis
									Lupus Vulgaris								
1	7.40	....	....	56.6	6.3	9.1	19.0	2.7	6.3	4.19	0.47	0.67	1.41	0.20	0.47	54 yr.	.....
2	6.96	....	....	52.1	6.4	9.5	14.6	3.2	14.4	3.63	0.44	0.66	1.02	0.22	1.00	30 yr.	.....
									Erythema Induratum								
1	7.72	4.67	3.05	44.9	5.6	9.2	11.9	2.7	25.7	3.47	0.43	0.71	0.92	0.21	1.98	11 yr.	.....
									Sarcoidosis								
1	8.18*	3.82	3.96	43.6	3.6	13.5	12.7	8.9*	17.9	3.56	0.29	1.10	1.04	0.73*	1.46	5 yr.	.....
2	9.63	....	....	42.9	5.6	8.2	16.7	3.0	23.6	4.13	0.54	0.79	1.60	0.29	2.27	21 yr.	Before treatment with vitamin D
..	8.00	4.30	3.70	52.2	5.3	7.9	13.7	3.3	17.8	4.17	0.42	0.63	1.09	0.26	1.42	.....	After 3 mo. of treatment with vitamin D
..	8.20*	....	....	46.1	4.7	7.0	14.4	8.4*	19.4	3.78	0.49	0.57	1.18	0.69*	1.59	.....	3 mo. after discontinuance of vitamin D
3	7.72	3.64	4.08	34.7	12.8	13.3	15.4	5.3	18.5	2.68	0.99	1.03	1.19	0.41	1.43	12 yr.	Extensive pulmonary involvement
									Lymphogranuloma Venereum								
1	7.50	....	....	45.4	6.8	8.4	16.4	4.2	18.8	3.41	0.51	0.63	1.23	0.32	1.41	6 wk.	.....
									Primary Familial Xanthomatosis								
1	7.50	8.90†		51.7	5.5	7.3	21.4	2.2	11.9	4.60	0.49	0.65	1.90	0.20	1.06	.....	Before ether extraction
..	....	7.30†		58.0	2.9	11.3	11.6	2.6	13.7	4.23	0.21	0.82	0.85	0.19	1.00	.....	After ether extraction
2	7.55	9.88†		42.4	3.5	45.1		2.1	6.8	4.19	0.35	4.46		0.21	0.67	.....	Before ether extraction
..	7.59	7.14†		54.8	4.7	12.3	11.3	3.6	13.2	3.91	0.34	0.88	0.81	0.26	0.94	.....	After ether extraction
3	6.56*	7.26†		48.4	7.3	6.5	23.1	6.5*	8.2	3.51	0.53	0.47	1.68	0.47*	0.60	.....	Before ether extraction
..	6.68*	6.71†		49.6	10.0	13.4	10.3	6.1*	10.5	3.33	0.67	0.90	0.69	0.41*	0.70	.....	After ether extraction
4	7.10	7.90†		53.2	3.9	11.9	18.9	2.7	9.4	4.20	0.31	0.94	1.49	0.21	0.74	.....	Before ether extraction
									Biliary Xanthomatosis								
1	7.10	11.74†		22.9	4.6	7.9	20.3	33.1	11.2	2.68	0.54	0.93	2.38	3.88	1.33	7 yr.	Before ether extraction
..	....	7.70†		36.7	3.4	18.7	14.9	6.3	20.0	2.82	0.26	1.44	1.15	0.49	1.54	.....	After ether extraction
2	8.71	10.54†		27.5	5.4	9.9	35.1		22.3	2.90	0.57	1.04	3.70		2.35	5 yr.	Before ether extraction
..	7.02	7.56†		34.3	5.5	12.3	13.8	3.4	30.9	2.59	0.42	0.93	1.04	0.26	2.34	.....	After ether extraction
									Myxedema Circumscriptum								
1	7.32	....	....	48.2	6.5	10.4	16.4	5.8	12.7	3.53	0.48	0.76	1.20	0.42	0.93	3 yr.	.....
									Lymphoma								
1	6.07*	3.04	2.42	39.3	7.6	9.8	11.7	12.5*	19.2	2.39	0.46	0.59	0.71	0.75*	1.16	10 yr.	Mycosis fungoides, tumor stage
2	6.59	....	....	47.6	6.2	8.9	16.4	3.7	17.4	3.14	0.41	0.59	1.08	0.24	1.15	2 yr.	Mycosis fungoides, tumor stage
3	7.22	....	....	50.3	6.4	8.8	15.1	3.6	16.0	3.63	0.46	0.64	1.09	0.26	1.16	6 yr.	Mycosis fungoides, tumor stage
4	7.37	....	....	52.9	6.7	10.8	13.9	2.4	13.5	3.90	0.49	0.80	1.02	0.18	0.99	3 mo.	Hodgkin's disease

* Determination includes fibrinogen.
† Determination of total protein by refractometry. The calculation of the absolute electrophoretic values in the patients with xanthomatosis is based on the refractometric values.

panied with considerable oozing, a moderate diminution of the total protein and of the albumin fraction was found with an occasional increase in the globulin fraction.[8] Very severe cases of generalized eczema showed a considerable reduction of the total protein and of the albumin fraction. In some instances the albumin fraction was reduced to values below 2.5 Gm. per 100 ml. of serum.[9] A study of infants with severe eczema [10] revealed moderately decreased values for total protein, with the albumin fraction markedly lowered and the globulin fraction increased.

Our Observations: Our study included eight patients with eczema (table 1). Two patients had extensive seborrheic dermatitis; two had atopic eczema, one of them localized and the other extensive; one had extensive dermatitis medicamentosa caused by gold, and three had generalized exfoliative dermatitis of unknown cause.

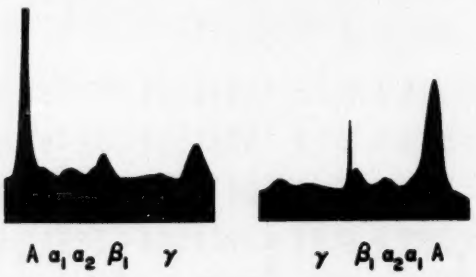

Fig. 1.—Normal electrophoretic pattern. The ascending pattern is on the left and the descending pattern on the right. The highest peak in each pattern represents the albumin.

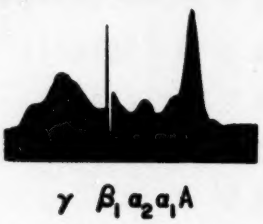

Fig. 2.—Descending pattern of a patient with generalized exfoliative dermatitis of unknown cause. The gamma peak is greatly increased in size. (For exact data see table 1, eczema, patient 6.)

None of the patients were seriously ill. One patient showed moderate hypoproteinemia, of 5.48 Gm. per 100 ml. of serum; the other seven had either normal or only slightly lowered values for total protein. Changes in the electrophoretic pattern were present in all patients with the exception of the one patient with localized atopic eczema (case 4). The albumin was decreased in all seven patients with extensive eczema. The decrease was slight to moderate in five and severe in two.

8. (*a*) Footnote 7. (*b*) Petersen, V. P., and Schønheyder, F.: Hypoproteinemia as a Complication in Universal Skin Diseases, Acta dermat.-venereol. **27**:497, 1947.

9. Cerutti.[7a] Petersen and Schønheyder.[8b]

10. Ribadeau-Dumas, L.; Lévy, M.; Dupuy, Y., and Mignon, S.: Les troubles du métabolism de l'eau chez les nourrissons eczémateux, Nourrisson **17**:65, 1929.

In the latter two patients (cases 1 and 6) the relative values for albumin were 35.2 and 31.3 per cent, respectively. The alpha-1 globulin value was slightly increased in four patients and moderately increased in two. The values in the latter two patients were 9.9 and 10.8 per cent, respectively. The gamma globulin showed moderate to considerable elevation in all seven patients with extensive eczema. The relative value for gamma globulin was greater than 20 per cent in three patients; in one patient (case 6) it amounted to 34.7 per cent, more than three times the normal value (figs. 1 and 2).

Psoriasis.—Review of Literature: No previous electrophoretic data on psoriasis were found. Studies of the total protein level and determination of the albumin and globulin fractions with the Howe method [7a,c] had revealed normal values.

Our Observations: Six patients with severe psoriasis were studied. One patient (case 1) with extensive plaques of psoriasis had a normal amount of total protein and an essentially normal electrophoretic pattern. The other five patients had generalized psoriatic erythroderma, in two of them (cases 4 and 5) associated with rheumatoid arthritis. The total protein was moderately decreased in all but one. The electrophoretic pattern showed in three of the five patients as only abnormality a slight rise of the alpha globulins (fig. 3). One patient (case 5) in whom the

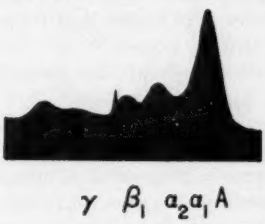

Fig. 3.—Descending pattern of a patient with generalized erythrodermic psoriasis. The alpha-1 and alpha-2 peaks are moderately increased in size. The gamma globulin peak is normal in size. (For exact data see table 1, psoriasis, patient 4.)

disease was very severe showed a considerable rise of the alpha globulins to a value of 27 per cent. In this patient plasma rather than serum was studied on two occasions, there being thus revealed a slight increase in fibrinogen. Finally, one patient (case 6) showed, in addition to a slight increase in alpha-1 globulin, an increase in the gamma-globulin to 16.0 per cent. This patient was 72 years of age, and it is possible that the increase in gamma globulin was due to his age rather than to psoriasis.

Burns.—Review of Literature: Robert [6] reported electrophoretic data on three patients with burns of second to third degree. Hypoproteinemia, amounting to 5.9 Gm. per 100 ml. of serum, was present only in the severest case. The electrophoretic pattern showed in all three patients a moderate decrease in the albumin; the alpha globulins were considerably increased, from a normal of 11 per cent to an average of 24 per cent. On the other hand, the amount of gamma globulin was slightly decreased.

Our Observations: We made no observations on burns.

RESULTS OF ELECTROPHORETIC ANALYSES IN PEMPHIGUS

Pemphigus Vulgaris.—Review of Literature: The protein analyses reported in the literature as well as our own determinations on patients with pemphigus vulgaris have been reported in a separate communication.[5]

Our Observations: Considerable changes in the concentration of the total protein and in the electrophoretic pattern were found to occur in patients with the malignant type of pemphigus vulgaris (pemphigus vulgaris acutus) during the advanced stage of the disease.[5] The changes were slight in the early stage of the disease and gradually became more pronounced with the advance of the disease. The early changes consisted in a slight decrease in the total protein and in the albumin and a slight increase in the alpha-1 and alpha-2 globulins. In the advanced stage of the disease the total protein showed a moderate, and occasionally a marked, decrease. In four of seven patients the total protein was decreased to values of 5 Gm. per 100 ml. of serum or less. The electrophoretic analyses showed a considerable decrease in the albumin. The values for albumin ranged in the seven patients who were examined in the advanced stage of the disease from 25.4 per cent down to 16.2 per cent, for an average of 22.1 per cent. The values for the alpha-1 and alpha-2 globulins were found to be decidedly increased. In five of the seven patients the relative value for the alpha globulins exceeded 30 per cent, and in two instances the values for alpha-2 globulin were higher than those for the albumin, a finding not observed in any other disease studied by us. The relative values for beta-1 and beta-2 globulins were usually normal. The amount of gamma globulin tended to increase slowly with the duration of the disease; in three patients in whom the disease had been in the advanced stage for several months the relative amount of gamma globulin was increased from a normal value of 11 per cent to values greater than 30 per cent. The decrease in the amount of albumin was even more apparent when the relative electrophoretic values were converted into absolute values per 100 ml. of blood serum. While normally the absolute amount of albumin per 100 ml. of serum, as determined by electrophoresis, averages 3.74 Gm., the lowest values obtained in the seven patients who were examined in the advanced stage of pemphigus vulgaris acutus ranged from 1.52 to 0.76 Gm., with an average value of 1.16 Gm.

In seven patients with the less severe type of pemphigus vulgaris, pemphigus vulgaris chronicus, the changes in total protein concentration and in the electrophoretic pattern were similar to those in pemphigus vulgaris acutus but were much less pronounced.

Since albumin is an important fraction of the serum protein concerned especially with the regulation of the osmotic equilibrium between the blood and the tissue fluids,[5] the possibility was considered by us that the marked reduction of the serum albumin in pemphigus vulgaris acutus was at least a contributing factor in the death of some of the patients. Five patients with severe pemphigus vulgaris acutus and appreciable hypoalbuminemia were therefore treated with infusions of human serum albumin.[11] Administration of adequate amounts of albumin resulted in an appreciable rise in the level of the serum albumin, as measured by electrophoresis, and in

11. Lever, W. F., and MacLean, J. G.: The Proteins in Pemphigus Vulgaris: III. The Effect of Infusions of Human Serum Albumin on the Proteins in the Blood Serum of Patients with Pemphigus Vulgaris, J. Invest. Dermat. **15**:215, 1950.

a temporary improvement of the general condition of the patients. However, no direct effect on the disease was noted. It was concluded that infusions of albumin are indicated as a supporting treatment in patients with severe hypoalbuminemia due to pemphigus.

Pemphigus Foliaceus.—Review of Literature: No electrophoretic analyses of pemphigus foliaceus patients have been reported so far. Studies of the total protein and of the Howe fractions have been reported on a total of seven patients.[12] The amount of total protein was normal in three patients, while in two it was moderately decreased, to values below 6 Gm., and in two markedly decreased, to values below 5.0 Gm. per 100 ml. of serum. The albumin fraction showed slightly or moderately decreased values. The globulin fraction varied from normal to moderately increased values.

Our Observations: In three patients the disease was in the active stage, with involvement of the entire skin surface, while in one patient it was in the late stage, having been present for 32 years. The values for total protein were below normal in all three patients who had the active stage of the disease. The albumin was

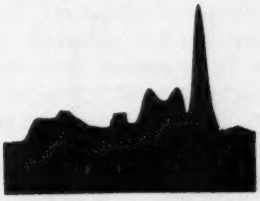

Fig. 4.—Descending pattern of a patient with pemphigus vegetans. The albumin peak is decreased in size. The alpha-1 and alpha-2 peaks show considerable increase and the gamma globulin peak moderate increase in size. (For exact data see table 1, pemphigus vegetans, patient 1, third determination.)

moderately or considerably decreased in all four patients, to values ranging from 33.9 to 39.3 per cent. The alpha globulins were consistently increased. In one patient the amount of the alpha globulins exceeded 30 per cent. The fibrinogen was increased in both patients for whom it was determined. The gamma globulin was near to normal in the one patient who had had the disease the shortest time. It seemed to increase with the duration of the disease, since in the two patients in whom the disease had been present for over a year it measured 19.6 and 20.5 per cent, respectively.

Pemphigus Vegetans.—Review of Literature: No electrophoretic analyses in pemphigus vegetans have so far been reported. Studies of the total protein and of the albumin and globulin fractions by the Howe method were carried out in a total

12. (*a*) Cerutti.[7a] (*b*) Mulvehill.[7c] (*c*) Brøchner-Mortensen, K.: Hypoproteinemia in Chronic Pemphigus, Acta med. scandinav. **97**:329, 1938. (*d*) Riordan, T. J.; Combes, F. C.; Costello, M. J., and Tulipan, L.: Pemphigus Treated with Carbarsone at Bellevue Hospital, Arch. Dermat. & Syph. **57**:532 (March) 1948.

of six cases.[13] The total protein was normal in one, while in three it was moderately decreased, to values below 6 Gm., and in two patients markedly decreased, to values below 5 Gm. per 100 ml. of serum. The albumin fraction was decreased slightly in one and decidedly in five, averaging 2.5 Gm. per 100 ml. of serum. The globulin fraction was moderately increased, averaging 3.0 Gm. per 100 ml. of serum.

Our Observations: Two patients were examined. The first patient had a moderately severe form of the disease of six weeks' duration, and the second patient had a mild form of the disease of 1½ years' duration. In both patients the total protein was moderately decreased. The electrophoretic pattern of the first patient (fig. 4) showed a rather decided decrease in the albumin (35.0 per cent), moderate increases in the alpha-1 and alpha-2 globulins (14.7 and 17.0 per cent, respectively) and a moderate increase in the gamma globulin (19.5 per cent). In the second patient the albumin was slightly decreased (40.7 per cent), the alpha-1 globulin slightly increased (8.3 per cent) and the gamma globulin considerably increased (23.3 to 25.1 per cent).

RESULTS OF ELECTROPHORETIC ANALYSES IN ALLERGIC DISEASES

Erythema Multiforme.—Review of Literature: No electrophoretic determinations for erythema multiforme have been published. Total protein determinations and fractionation with the Howe method were carried out in five cases of erythema multiforme bullosum by Mulvehill.[7c] One person showed a slight decrease in the total protein and in the albumin fraction. The other patients had essentially normal values.

Our Observations: Four cases were studied. Two patients (cases 1 and 2) had a moderately extensive, bullous eruption of short duration with only slight impairment of the general health. One patient (case 3) had severe erythema multiforme of the Stevens-Johnson type but recovered quickly. In the fourth patient the disease was caused by hypersensitivity to phenolphthalein, was severe and ended fatally. In the first two patients the total protein was normal and the electrophoretic patterns showed as only abnormality a slight increase in the amount of gamma globulin. The patient with the Stevens-Johnson type of erythema multiforme presented a normal total protein and a slight increase in the amounts of the alpha-1 and alpha-2 globulins. The fourth patient had a decided decrease in the total protein, to 5.0 Gm. per 100 ml. The electrophoretic pattern showed a moderate decrease in the albumin (34.2 per cent) and moderate increases in the alpha-1 globulin (11.8 per cent), the alpha-2 globulin (13.6 per cent) and the gamma globulin (19.9 per cent).

Blister Fluid: In three patients total protein determination and electrophoretic analyses were carried out not only on blood serum but also on blister fluid. Comparison of the data obtained on blister fluid and on the corresponding blood serums gave results similar to those obtained by us in a study of blister fluid in pemphigus vulgaris.[14] In all three patients with erythema multiforme the concentration of the

13. Cerutti.[7a] Mulvehill.[7c] Riordan, Combes, Costello and Tulipan.[12d]

14. Lever, W. F.: The Proteins in Pemphigus Vulgaris: II. Electrophoretic Analysis of the Proteins in the Blister Fluid of Patients with Pemphigus Vulgaris, J. Invest. Dermat. **14**: 219, 1950.

total protein was lower in the blister fluid than in the corresponding blood serum. The electrophoretic patterns of the blister fluid resembled those of the corresponding blood serums closely. However, in spite of the correlation between the electrophoretic patterns, the relative concentrations of albumin and beta-2 globulin were slightly higher and the relative concentration of beta-1 globulin was slightly lower in the blister fluid than in the corresponding blood serum; also, as had already been observed in several instances of pemphigus vulgaris, the electrophoretic pattern of the blister fluid showed in one patient the beta-2 globulin value as a small peak (fig. 5), whereas in the pattern of the corresponding blood serum it was represented merely by a plateau that in part filled the valley between the beta-1 peak and the gamma peak.

Dermatitis Herpetiformis.—Review of Literature: Robert [6] reported electrophoretic analyses of two cases of dermatitis herpetiformis. In both patients the values for total protein were normal. The electrophoretic patterns showed a slight decrease in albumin and a slight increase in the alpha globulins.

Determinations of total protein and of the Howe fractions have been reported on a total of 17 cases.[8] In most cases the values for total protein were normal or

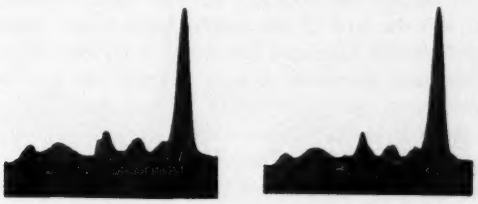

Fig. 5.—Descending patterns of the blood serum (left) and of the corresponding blister fluid (right) of a patient with bullous erythema multiforme. The two patterns resemble each other greatly. Both are essentially normal except for a slight increase in the size of the gamma globulin peak. Note that the pattern of the blister fluid shows a small beta-2 peak which is absent in the pattern of the blood serum.

slightly below normal, but in a few there was a distinct hypoproteinemia with lowering of the albumin fraction. In several cases the globulin fraction was moderately increased.

Our Observations: Five patients were examined. All were in good general condition. One patient, aged 72, had slight hypoproteinemia; the others had normal values for total protein. No significant abnormalities were present in any of the electrophoretic patterns.

Erythema Nodosum.—Review of Literature: Malmros and Blix [15] have reported electrophoretic analyses of nine cases of erythema nodosum. The values for total protein were normal. The amount of albumin was moderately decreased in all instances. Most cases showed a moderate increase in the alpha globulins.

15. Malmros, H., and Blix, G.: The Plasma Proteins in Cases with High Erythrocyte Sedimentation Rate, Acta med. scandinav. (supp.) **170**:280, 1946.

Two of the patients had increased amounts of gamma globulin, namely 37.5 and 45.5 per cent, respectively. The amount of fibrinogen, determined by the salting-out method, was clearly above normal in all patients.

Determination of the Howe fractions by Favour and Sosman [16] in six patients revealed normal values for albumin and globulin in four patients. In two patients the globulin fraction was elevated to 4.5 and 5.2 Gm. per 100 ml. of serum, respectively.

Our Observations: In one patient with erythema nodosum of six weeks' duration moderate elevations of the alpha-1 globulin (7.0 per cent), alpha-2 globulin (15.4 per cent) and gamma globulin (15.7 per cent) were found with a corresponding decrease in the albumin (42.9 per cent).

RESULTS OF ELECTROPHORETIC ANALYSES IN COLLAGEN DISEASES

Lupus Erythematosus.—Review of Literature: Electrophoretic analyses in lupus erythematosus have been reported by Coburn and Moore [17] and by Walker and Benditt.[18] Coburn and Moore investigated two cases. In the first case, in which the disease was in the active stage, the gamma globulin was very high, measuring 45.8 per cent, while the other globulins were approximately normal. In the second case the disorder had been in a quiescent state for three years preceding the examination; still the level of the gamma globulin was elevated to 31.5 per cent. Walker and Benditt examined four cases of chronic discoid, five cases of subacute disseminate and four cases of acute systemic lupus erythematosus. The total protein values were consistently within normal limits. The electrophoretic pattern showed in all three types a significant elevation of the gamma globulin values averaging 18.2 per cent in the chronic discoid type, 23.6 per cent in the subacute disseminate type and 32.3 per cent in the acute systemic type as compared with a normal value of 12.9 per cent. The values for albumin showed a corresponding decrease. In addition, there was in acute systemic lupus erythematosus a decrease in the beta globulin concentration. No significant changes occurred in the alpha globulin values.

Total protein determinations and Howe fractionation studies were carried out on 15 patients by Coburn and Moore.[17] The total protein values were within normal limits. In all patients the albumin fraction was decreased and the globulin fraction increased to such an extent that the albumin-globulin ratio was reversed. The mean values in the 15 patients were as follows: for total protein, 7.0 Gm.; for the albumin fraction, 3.1 Gm., and for the globulin fraction, 3.9 Gm. per 100 ml. of serum.

Our Observations: Our investigations concern three cases of chronic discoid lupus erythematosus, two cases of subacute disseminate lupus erythematosus and seven cases of acute systemic lupus erythematosus.

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16. Favour, C. B., and Sosman, M. C.: Erythema Nodosum, Arch. Int. Med. **80**:435 (Oct.) 1947.

17. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196, 1943.

18. Walker, S. A., and Benditt, E. P.: The Serum Proteins in Diseases of Connective Tissue, J. Invest. Dermat. **14**:113, 1950.

The three patients with chronic discoid lupus erythematosus had normal levels of total protein. The electrophoretic patterns were normal except for a slight elevation of the alpha-1 and alpha-2 globulins, to 7.7 and 13.6 per cent, in the first case, and a slight elevation of the gamma globulin, to 13.8 per cent, in the third case. In the latter case the eruption was extensively distributed over face, scalp, chest and arms and showed moderate activity.

In the two patients with subacute disseminate lupus erythematosus the values for total protein were normal. The electrophoretic pattern showed a moderate increase in gamma globulin, to 14.2 and 17.4 per cent, respectively, and a corresponding decrease in albumin.

In the seven cases of acute systemic lupus erythematosus the total protein values varied. In two patients the values were normal; in two patients who were in a serious condition the total protein was lowered to 5.0 Gm. and 4.95 Gm. per 100 ml. of serum, respectively, and in three the total protein was higher than normal, namely 7.72, 7.86 and 8.0 Gm., respectively, the increase being the result of hypergammaglobulinemia, as the electrophoretic pattern showed. Electrophoretic analysis in the seven patients revealed consistently an increase in gamma globulin

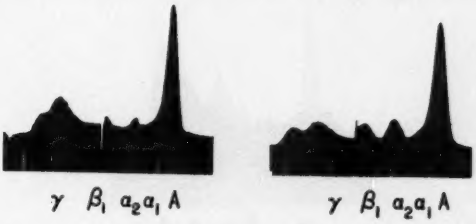

Fig. 6.—Descending patterns of a patient with acute systemic lupus erythematosus before treatment with ACTH (left) and after treatment (right). Before treatment the gamma globulin peak is greatly increased in size. After treatment it is only slightly larger than normal. (For exact data see table 1, acute systemic lupus erythematosus, patient 4, first and fifth determinations.)

and a decrease in albumin. By taking the highest value for gamma globulin in each of the seven patients an average of 27.1 per cent was obtained. It is noteworthy that the increase in the amount of gamma globulin occurred early in the disease: one patient in whom the disease had been active for only three weeks showed a gamma globulin value of 18.2 per cent, and two patients who had had the disease for only two months showed values of 19.2 and 28.4 per cent, respectively. The alpha-1 globulin was slightly increased in several patients while the beta-1 globulin showed a fairly consistent, though slight, decrease. The average values in the seven patients for alpha-1 globulin were 6.1 per cent; for alpha-2 globulin, 9.8 per cent, and for beta-1 globulin, 12.2 per cent.

In one patient with acute systemic lupus erythematosus the effect of treatment with adrenocorticotropic hormone (ACTH) on the electrophoretic pattern was studied.[19] During two courses of ACTH, extending over 13 and nine days, respec-

19. Thorn, G. W.; Bayles, T. B.; Massell, B. F.; Forsham, P. H.; Hill, S. J.; Smith, S., III, and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**:529, 1949.

tively, and given during a period of 43 days, the gamma globulin gradually fell from 28.4 to 18 per cent, or, expressed in absolute values, from 2.27 to 1.18 Gm. per 100 ml. of serum (fig. 6). Striking clinical improvement was evident before any significant change in the circulating gamma globulin had occurred.

Dermatomyositis.—Review of Literature: Walker and Benditt [18] examined by electrophoresis the serum of four patients with dermatomyositis. They found a moderate decrease in total protein, to an average value of 5.73 Gm. per 100 ml. The albumin was decreased to an average of 47.3 per cent, or 2.27 Gm. per 100 ml. The values for the alpha and beta globulins were within the normal range. The gamma globulin, in contrast to the situation in lupus erythematosus, showed no absolute increase. However, in relative values, the gamma globulin in the four patients averaged 17.8 per cent as compared with a normal value of 12.9 per cent.

Our Observations: Three patients were examined. All three were severely ill. The first patient, who had a fulminating form of the disease, had severe hypoproteinemia of 4.1 Gm. per 100 ml. of serum. The albumin was considerably decreased, to 28.9 per cent, and the values for alpha-1 and alpha-2 globulins were greatly increased, to 19.0 and 25.9 per cent, respectively. The amount of gamma globulin was normal (fig. 7). The second patient showed during the active stage

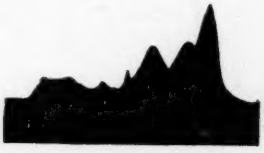

Fig. 7.—Descending pattern of a patient with dermatomyositis. The albumin peak is smaller than normal. The alpha-1 and alpha-2 globulin peaks are greatly increased in size. The gamma globulin peak is normal. (For exact data see table 1, dermatomyositis, patient 1.)

of the disease slight hypoproteinemia, a slight decrease in albumin, slightly increased values for alpha-1 and alpha-2 globulins and a normal gamma globulin. A year and a half later, while still chronically ill, the patient showed an electrophoretic pattern which was normal except for a slight increase in the alpha-2 globulin. The third patient, whose disease terminated fatally shortly after the second electrophoretic determination, showed moderate hypoproteinemia, a moderate decrease in albumin and slightly increased values for alpha-1 and alpha-2 globulins. In contrast to observations in the other two patients, the gamma globulin was moderately increased, both relatively and absolutely. Analysis on two occasions revealed relative values for gamma globulin of 19.1 and 18.3 per cent and absolute values of 1.05 and 1.18 Gm. per 100 ml. of serum.

Scleroderma.—Review of Literature: Walker and Benditt [18] have reported electrophoretic analyses on six patients with circumscribed and eight patients with diffuse scleroderma. No change in the total protein concentration was observed in either type of scleroderma. In the patients with circumscribed scleroderma the electrophoretic pattern revealed a slight decrease in albumin. The gamma globulin

varied. In most cases there was an increase, but in one case there was a distinct decrease in the gamma globulin concentration. The patients with diffuse scleroderma showed consistently a decrease in the albumin concentration and an increase in the gamma globulin concentration. The gamma globulin showed, on the average, an absolute value of 1.46 Gm. per 100 ml. and a relative value of 21.6 per cent.

Our Observations: Three patients with circumscribed scleroderma were examined. All had normal values for total protein. Two had normal electrophoretic patterns. The third patient, in whom the lesions were extensive, showed a slight increase of the alpha-2 globulin, to 13.5 per cent, and of the gamma globulin, to 13.1 per cent.

Eight patients with diffuse scleroderma were examined. Two showed a slight decrease and two a decided increase in total protein concentration, to 8.38 and 8.66 Gm. per 100 ml., respectively. The increase in total protein was the result of a marked increase in gamma globulin. The electrophoretic patterns obtained varied with the stage and the severity of the disease. Two patients (cases 1 and 2) who had a fairly mild form of the disease, characterized mainly by acrosclerosis, displayed essentially normal patterns. One patient (case 3) who had a rather fulminating

Fig. 8.—Descending pattern of a patient with diffuse scleroderma. The gamma globulin peak is greatly increased in size. (For exact data see table 1, generalized scleroderma, patient 8.)

form of the disease, with relatively mild cutaneous but marked visceral involvement, displayed high values for the alpha-1 and alpha-2 globulins (10.3 and 17.4 per cent, respectively), while the amount of gamma globulin was normal. The other five patients had extensive cutaneous involvement as well as visceral lesions. They all showed striking elevation of the gamma globulin, averaging 25.5 per cent, and a corresponding decrease in the concentration of albumin (fig. 8). There was a slight elevation of the alpha-1 globulin in one and of the alpha-2 globulin in another of these patients.

Five patients received treatment with ACTH.[20] The gamma globulin decreased to a significant degree in all. In the two patients (cases 1 and 2) who had had normal values for gamma globulin before the treatment, the amount decreased to subnormal values. In four of the five patients there was a decrease in total protein corresponding to the decrease in gamma globulin.

20. Bayles, T. B.; Stout, C. F.; Stillman, J. S., and Lever, W. F.: The Treatment of Scleroderma with Adrenocorticotropic Hormone: Preliminary Observations, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 447.

RESULTS OF ELECTROPHORETIC ANALYSES IN INFECTIOUS DISEASES

Lupus Vulgaris.—Review of Literature: No electrophoretic analyses on patients with lupus vulgaris have been reported. Midana [7b] reported total protein determinations and Howe fractionation studies in eight cases of lupus vulgaris. The average values for total protein were slightly above normal (7.25 Gm. per 100 ml. of serum). The albumin fraction was slightly decreased (3.26 Gm. per 100 ml.) and the globulin fraction considerably increased (3.86 Gm. per 100 ml.), a reversal of the albumin-globulin ratio resulting. These values correspond to the electrophoretic values reported by Seibert and co-workers [21] for active, moderately advanced pulmonary tuberculosis. The average values obtained by these authors [21b] on 22 patients were as follows: total protein 7.67 Gm. per 100 ml.; albumin, 43.5 per cent; alpha-1 globulin, 8.5 per cent; alpha-2 globulin, 12.2 per cent; beta globulin, 14.8 per cent, and gamma globulin, 21.2 per cent.

Our Observations: Two patients with long-standing but nearly arrested lupus vulgaris of the face were examined. The first patient had a low normal amount and the second patient a slightly increased amount of gamma globulin. All other values were normal.

Erythema Induratum.—Review of Literature: No analyses of the serum proteins in erythema induratum were found in the literature.

Our Observations: In the one patient examined the total protein was slightly increased, to 7.72 Gm. per 100 ml. The albumin was slightly decreased, to 44.9 per cent, and the gamma globulin considerably increased, to 25.7 per cent. The values for the alpha and beta globulins were normal.

Sarcoidosis.—Review of Literature: Electrophoretic analyses on sarcoidosis have been reported by Fisher and Davis [22] and by Seibert and co-workers.[21] Fisher and Davis examined eight active and four inactive cases. Of the eight active cases four had hyperproteinemia, with values of total protein above 8 Gm. per 100 ml. The albumin level was found to be slightly lowered. The gamma globulin readings were elevated in seven of the eight cases, exceeding 30 per cent in five patients. The amounts of the alpha and beta globulins were normal. The inactive cases presented slightly lowered values for albumin; the gamma globulin was normal in one and slightly elevated in three. A slight increase in the alpha globulins, not noted in the active cases, was present in three of the four inactive cases. Seibert and co-workers reported in two publications electrophoretic analyses of six and 11 cases, respectively. The data confirmed Fisher and Davis's findings of hyperproteinemia, hypoalbuminemia and hypergammaglobulinemia. In their second series [21b] the following average values were determined: for total protein, 7.88 Gm. per 100 ml. of serum; for albumin, 39.4 per cent, and for gamma globulin, 26.1 per cent. The values for the alpha-1 and alpha-2 globulins were normal, but a slight rise in the beta globulins to 15.9 per cent, from a normal value of 13.8 per cent, was noted.

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21. (*a*) Seibert, F. B., and Nelson, J. W.: Electrophoresis of Serum: Serum Proteins in Tuberculosis and Other Chronic Diseases, Am. Rev. Tuberc. **47**:66, 1943. (*b*) Seibert, F. B.; Seibert, M. V.; Atno, A. J., and Campbell, H. W.: Variation in Protein and Polysaccharide Content of Sera in the Chronic Diseases: Tuberculosis, Sarcoidosis and Carcinoma, J. Clin. Invest. **26**:90, 1947.

22. Fisher, A. M., and Davis, B. D.: The Serum Proteins in Sarcoid: Electrophoretic Study, Bull. Johns Hopkins Hosp. **71**:364, 1942.

Even before electrophoretic analysis became available the existence in sarcoidosis of hyperproteinemia, hypoalbuminemia and hyperglobulinemia had been established by use of the Howe fractionation. Salvesen,[23] in 1935, first called attention to these changes, describing three cases with total protein values over 9 Gm. and with the globulin fraction larger than 5.0 Gm. per 100 ml. of serum. Harrell and Fisher [24] obtained the following average values in 18 determinations on 11 cases: total protein, 8.0 Gm.; albumin fraction, 3.30 Gm., and globulin fraction, 4.78 Gm. per 100 ml. Gutman and co-workers,[25] in a study of five cases, reported similar values.

Our Observations: Three patients with sarcoidosis were studied: two had predominantly cutaneous lesions and were in good general condition, while the third patient had severe pulmonary involvement and was in poor general condition. The first two patients had considerable hyperproteinemia, of 8.18 and 9.63 Gm. per 100 ml., respectively. The electrophoretic pattern in these two patients revealed slight relative hypoalbuminemia, but the absolute albumin values were normal: 3.56 and 4.13 Gm., respectively. Both patients presented quite markedly increased values for gamma globulin (17.9 and 23.6 per cent, respectively). In the first patient there was also a slight increase in the alpha-2 globulin, to 13.5 per cent. The third patient had a moderate hyperproteinemia, of 7.72 Gm. per 100 ml. of serum. The albumin was decreased, relatively as well as absolutely. The alpha-1 globulin was decidedly increased (12.8 per cent) and the alpha-2 globulin slightly increased (13.3 per cent). The gamma globulin showed a considerable increase (18.5 per cent).

The second patient was treated with massive doses of vitamin D, consisting of 150,000 to 300,000 units per day. Within three months a pronounced decrease in the amount of total protein and of gamma globulin occurred. The gamma globulin decreased from 23.6 to 17.8 per cent or, expressed in absolute values, from 2.27 to 1.42 Gm. per 100 ml. The cutaneous lesions showed considerable improvement during this period.

Leprosy.—Review of Literature: Seibert and Nelson [21a] reported electrophoretic analyses on three patients with advanced leprosy. The total protein averaged 7.93 Gm. per 100 ml. The albumin showed a moderate decrease, to 43.2 per cent, while the alpha and gamma globulins were markedly increased, to more than twice their normal value.

Howe fractionation data on leprosy were first reported by Frazier and Wu.[26] In 31 cases the total protein averaged 8.68 Gm. per 100 ml. The albumin fraction was essentially normal, but the globulin fraction was greatly elevated, to more than twice the normal amount in lepromatous leprosy and to not quite twice the normal amount in maculoanesthetic leprosy. Cerutti [7a] found hyperproteinemia, a slight

23. Salvesen, H. A.: The Sarcoid of Boeck: A Disease of Importance to Internal Medicine, Acta med. scandinav. **86**:127, 1935.

24. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, J. Clin. Invest. **18**:687, 1939.

25. Gutman, A. B.; Moore, D. H.; Gutman, E. B.; McClellan, V., and Kabat, E. A.: Fractionation of Serum Proteins in Hyperproteinemia, with Special Reference to Multiple Myeloma, J. Clin. Invest. **20**:765, 1941.

26. Frazier, C. N., and Wu, H.: Blood Serum Globulin in Leprosy, Am. J. Trop. Med. **5**: 297, 1925.

lowering of the albumin fraction and a great increase in the globulin fraction, to twice its normal value, in two cases of "mixed leprosy." Midana [7b] found in six cases of leprosy normal values of total protein, a moderate decrease in the albumin fraction and a moderate increase in the globulin fraction. Faget and Ross [27] confirmed the tendency to hyperglobulinemia in an investigation of 126 cases of leprosy. About 60 per cent of the cases showed hyperglobulinemia, some to a marked degree. The values for total protein were for the most part within normal range. The albumin fraction varied from normal values to rather low levels.

Our Observations: We made no electrophoretic analyses in cases of leprosy.

Lymphogranuloma Venereum.—Review of Literature: A thorough electrophoretic study of lymphogranuloma venereum has recently been reported by Rottino, Suchoff and Stern.[28] Prior to that only a few electrophoretic analyses had been carried out, namely by Gutman and co-workers in one patient [25] and by Kabat, Moore and Landow [29] in two patients. In Gutman's case there was distinct hyperproteinemia, of 9.8 Gm. per 100 ml., caused by an enormous increase in the gamma globulin, to a value of 50.2 per cent. Kabat, Moore and Landow found in two cases increases in the gamma globulin to 34.3 and 38.4 per cent, respectively. Rottino, Suchoff and Stern divided their patients into three groups: Group A was comprised of patients with minimal clinical signs. In this group the electrophoretic patterns were esssentially normal except that the values for alpha-2 were slightly above normal. The patients of group B were bedridden and emaciated and had fever. They all died within three days to five months after the electrophoretic analysis. The electrophoretic patterns showed decidedly lowered values for albumin and significant increases in either alpha-1 globulin or alpha-2 globulin, or in both. The values for gamma globulin were slightly increased. Group C was composed of patients who were ambulatory but more severely affected than those of group A. In these patients the albumin was slightly lowered, the alpha-1 and alpha-2 globulins slightly increased and the gamma globulin markedly increased, to an average of 23.2 per cent.

Our Observations: One patient who had an active inguinal bubo and thus could be included in group C of Rottino's classification showed slight elevation of the total protein and an electrophoretic pattern like that attributed by Rottino to group C: a slight decrease in albumin, slight increases in alpha-1 and alpha-2 globulins and a considerable increase in gamma globulin, to 18.8 per cent.

Syphilis.—Review of Literature: Electrophoretic analyses of syphilis have been reported by Cooper, Craig and Beard [30] and by Benditt and Walker.[31] Cooper,

27. Faget, G. H., and Ross, H.: Evaluation of Positive Kolmer and Kahn Tests in Leprosy, Ven. Dis. Inform. **25**:133, 1944.

28. Rottino, A.; Suchoff, D., and Stern, K. G.: Electrophoretic Study of the Blood Serum from Lymphogranulomatous Patients, J. Lab. & Clin. Med. **33**:624, 1948.

29. Kabat, E. A.; Moore, D. H., and Landow, H.: An Electrophoretic Study of the Protein Components in Cerebrospinal Fluid and Their Relationship to Their Serum Protein, J. Clin. Invest. **21**:571, 1942.

30. Cooper, G. R.; Craig, H. W., and Beard, J. W.: Electrophoretic Analysis of Syphilitic, Biologic False Positive, and Normal Human Sera, Am. J. Syph., Gonor. & Ven. Dis. **30**:555, 1946.

31. Benditt, E. P., and Walker, S. A.: Serum Proteins in Syphilis: Electrophoretic Study, Am. J. Med. **4**:663, 1948.

Craig and Beard examined 28 serums from patients with syphilis and found the amounts of alpha-1 globulin slightly and of gamma globulin moderately higher than those in the serums of normal persons. The average value for gamma globulin was 21.6 per cent, as compared with 14.8 per cent in normal subjects. The value for albumin was decreased proportional to the increases in alpha-1 and gamma globulins. Benditt and Walker found the albumin moderately decreased and the gamma globulin concentration moderately increased in all stages of the disease. The beta globulin was not altered. The alpha-1 globulin was slightly increased in secondary syphilis, while the alpha-2 globulin was slightly increased in secondary as well as tertiary syphilis.

Our Observations: We made no electrophoretic analyses in cases of syphilis.

Pinta and Yaws.—Review of Literature: Dillon and Cooper [32] examined by electrophoresis the serums of three patients with pinta and of three patients with yaws.

The patients with pinta had moderate hyperproteinemia, averaging 8.48 Gm. per 100 ml. of serum. The electrophoretic patterns for these patients resembled those of the syphilitic serums studied by Cooper, Craig and Beard. The average amount of gamma globulin was 25.3 per cent, or 2.19 Gm. per 100 ml. of serum.

The patients with yaws had considerable hyperproteinemia, averaging 8.90 Gm. per 100 ml. of serum. The electrophoretic patterns for these patients revealed slight increases in the amounts of alpha-1 and alpha-2 globulins and a great increase in gamma globulin. The increase in gamma globulin was greater than that observed in syphilitic or pinta serums. The average amount of gamma globulin was 43.7 per cent, or 4.07 Gm. per 100 ml.

Our Observations: We made no observations on pinta or yaws.

RESULTS OF ELECTROPHORETIC ANALYSES IN METABOLIC DISEASES

Primary Familial Xanthomatosis.—Review of Literature: The electrophoretic findings in one patient studied by Zeldis and co-workers [33] and in two of our four patients have been reported in a recent communication.[34]

Our Observations: The four patients showed approximately normal values for all electrophoretic components except the beta-1 globulin. The amount of beta-1 globulin was considerably increased in three and moderately increased in one. In the patient with the greatest increase in beta-1 globulin (case 2) the beta-1 globulin peak occupied not only its own area in the electrophoretic pattern but also the area of alpha-2. Thus the beta-1 globulin migrated in the electric field with greater than normal speed.

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32. Dillon, M. L., and Cooper, G. R.: Electrophoretic Analysis of Serum from Patients with Pinta and Yaws, Am. J. Syph., Gonor. & Ven. Dis. **32**:251, 1948.

33. Zeldis, L. J.; Alling, E. L.; McCoord, A. B., and Kulka, J. P.: Plasma Protein Metabolism: Electrophoretic Studies; The Influence of Plasma Lipids on Electrophoretic Patterns of Human and Dog Plasma, J. Exper. Med. **82**:411, 1945.

34. Lever, W. F., and MacLean, J. G.: Primary Familial Xanthomatosis and Biliary Xanthomatosis (Biliary Cirrhosis with Xanthomatosis): Electrophoretic Studies, J. Invest. Dermat. **15**:173, 1950.

Extraction of the lipids with cold ether was carried out for three of the four patients. Electrophoretic analysis following this procedure revealed the beta-1 globulin component in all instances reduced to approximately normal size (fig. 9), proving that the increase in size had been caused by lipids which had united with proteins to form lipoproteins.

Of interest is the great discrepancy in the values for total protein obtained by the Kjeldahl method of nitrogen determination and by the refractometric method. This discrepancy is due to the fact that the method of nitrogen determination, in contrast to the refractometric method, does not take the lipid moieties of the lipoproteins into account.

Biliary Xanthomatosis (Biliary Cirrhosis with Xanthomatosis).—Review of Literature: The electrophoretic analyses reported in the literature as well as the findings for our two patients have been reported in a recent communication.[84]

Our Observations: The first patient showed, before extraction of the serum with cold ethyl ether, a reduced albumin peak, normal alpha-1 and alpha-2 peaks, greatly increased beta-1 and beta-2 peaks, and a normal gamma peak. The second patient showed, before extraction of the serum, a reduced albumin peak, normal

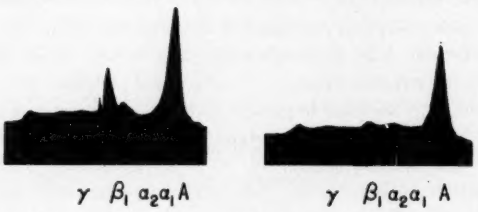

Fig. 9.—Descending patterns of a patient with primary familial xanthomatosis before (left) and after (right) extraction of lipids by cold ethyl ether. In the pattern on the left the beta-1 globulin peak is increased in size, while in the pattern on the right it is normal in size. (For exact data see table 1, primary familial xanthomatosis, patient 3.)

alpha-1 and alpha-2 peaks, a large massive beta-1 peak of reduced mobility occupying the area of beta-1 as well as of beta-2 and a large gamma peak.

After extraction of the lipids, both serums showed low albumin peaks, normal alpha-1, alpha-2, beta-1 and beta-2 peaks and markedly enlarged gamma peaks. This observation proved that the great increase in the size of the beta-1 and beta-2 peaks in the first patient and of the beta-1 peak in the second patient was caused by lipids which had united with proteins to form lipoproteins.

The patterns obtained for the two patients affected by biliary cirrhosis with xanthomatosis differed from those obtained for the patients with primary familial xanthomatosis in two ways: first, the beta-1 lipoprotein migrated with less than normal speed, and, second, after ether extraction the pattern showed a decrease in albumin and an increase in gamma globulin, explainable on the basis of parenchymatous damage to the liver, in connection with which this change is regularly observed. Just as in the patients with primary familial xanthomatosis, a great discrepancy existed between the total protein values obtained by the Kjeldahl method of nitrogen determination and those found by refractometry.

Myxedema.—Review of Literature: Electrophoretic data on five patients with myxedema have been reported by Lewis, McCullagh and Clark.[35] The total protein values were within the normal range. The albumin was slightly decreased, and the beta and gamma globulins were moderately increased. The average value for beta globulin was 18.0 per cent, as compared with 13.1 per cent in normal persons, and the average value for gamma globulin was 15.4 per cent, as compared with 11.7 per cent in normal persons. Robert[6] reported electrophoretic data on one patient with myxedema tuberosum. The data were similar to those reported by Lewis, McCullagh and Clark.

Our Observations: One patient with circumscribed (pretibial) myxedema showed a slight decrease in albumin, to 48.2 per cent. The beta-1 and gamma globulins were slightly, but not significantly, increased, to 16.4 and 12.7 per cent, respectively.

RESULTS OF ELECTROPHORETIC ANALYSES IN TUMORS

Lymphoma.—Review of Literature: Petermann, Karnofsky and Hogness[36] reported data on eight patients with Hodgkin's disease. Six patients who were in fair general condition had normal values for total protein, while two patients who were in the terminal stage had hypoproteinemia. The albumin was moderately lowered in the patients in fair condition and considerably lowered in the patients in the terminal stage. The alpha-1 and alpha-2 globulins were increased in seven out of eight cases. The fibrinogen was elevated in every case. The gamma globulin was moderately elevated in five of the six patients in fair condition and was normal in the two patients in the terminal stage. The only patient who had no increase in the alpha globulins had a very high value for gamma globulin, namely 44.8 per cent, or 4.13 Gm. per 100 ml. of plasma. This patient, though in fair condition, had intense pruritus and severe cutaneous changes associated with Hodgkin's disease. Robert[6] reported data on one patient with mycosis fungoides who was in the tumor stage of the disease. This patient had a normal value for total protein. There was a slight decrease in albumin and a slight increase in the alpha globulins and the gamma globulin.

Our Observations: Four patients were examined. Three had the tumor stage of mycosis fungoides and one had Hodgkin's disease associated with an extensive, pruritic, nonspecific cutaneous eruption. The first patient with mycosis fungoides was in a terminal state. He had moderate hypoproteinemia, of 5.46 Gm. per 100 ml. of serum. The albumin was moderately decreased, to 39.3 per cent, and the alpha and beta globulins were essentially normal, while the fibrinogen was increased to 12.5 per cent and the gamma globulin to 19.2 per cent. The other three patients were in a fair general condition. They showed as only abnormality a slight or moderate increase in the gamma globulin, to values of 17.4, 16.0 and 13.5 per cent, respectively.

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35. Lewis, L. A.; McCullagh, E. P., and Clark, J.: Electrophoretic Analysis of Plasma Proteins in Hyperthyroidism and Hypothyroidism, Am. J. M. Sc. **208**:727, 1944.

36. Petermann, M. L.; Karnofsky, D. A., and Hogness, K. R.: Electrophoretic Studies on the Plasma Proteins of Patients with Neoplastic Disease: III. Lymphoma and Leukemia, Cancer **1**:107, 1948.

COMMENTS

The abnormalities observed in the electrophoretic patterns of patients with various diseases reflect the patients' reactions to their diseases. Since patients affected by the same disease tend to react similarly, there is considerable consistency in the electrophoretic patterns obtained from patients with the same disease, and it is possible to associate a certain electrophoretic pattern with many diseases

TABLE 2.—*Trend of Electrophoretic Changes in Various Dermatoses*

	Total Protein	Albumin	α-1	α-2	β-1	Fibrinogen	γ
Inflammatory Diseases							
Extensive eczema	—	— —	+	(+)	....	..	++
Extensive psoriasis	(—)	—	+	+	....	+	....
Burns	—	— —	++	++	....	..	....
Pemphigus							
Pemphigus vulgaris acutus, early	—	—	+	+	....	..	....
Pemphigus vulgaris acutus, advanced	— —	— — —	++	++	....	+	+
Pemphigus vulgaris acutus, terminal	— —	— — —	+	+	....	..	++
Pemphigus vulgaris chronicus	—	—	+	+	....	..	+
Pemphigus foliaceus	—	— —	+	+	....	+	+
Pemphigus vegetans	—	— —	++	++	....	..	++
Allergic Diseases							
Erythema multiforme	—	—	+	+	....	..	+
Dermatitis herpetiformis	....	....	....	....	....	..	....
Erythema nodosum	....	—	+	+	....	+	(+)
"Collagen" Diseases							
Lupus erythematosus, chronic discoid	....	....	....	....	....	..	(+)
Lupus erythematosus, chronic disseminated	....	—	....	....	....	..	+
Lupus erythematosus, acute systemic	—	—	(+)	....	(—)	..	++
Dermatomyositis	—	—	++	++	....	..	(+)
Scleroderma, circumscribed	....	....	....	....	....	..	(+)
Scleroderma, diffuse	+	—	(+)	(+)	....	..	++
Infectious Diseases							
Lupus vulgaris	+	—	(+)	(+)	....	..	+
Erythema induratum	+	—	....	....	....	..	++
Sarcoidosis	++	—	(+)	(+)	....	..	++
Leprosy	++	—	+	+	....	..	++
Lymphogranuloma venereum, severe	—	— —	++	++	....	..	+
Lymphogranuloma venereum, chronic mild	++	—	+	+	....	..	++
Syphilis	....	—	(+)	(+)	....	..	+
Pinta	+	—	(+)	(+)	....	..	+
Yaws	++	—	(+)	(+)	....	..	++
Metabolic Diseases							
Primary familial xanthomatosis	+	—	....	(+)	++	..	....
Biliary xanthomatosis	+	— —	....	....	++	..	++
Myxedema	....	—	....	....	+	..	+
Myxedema circumscriptum	....	....	....	....	(+)	..	(+)
Tumors							
Mycosis fungoides	—	— —	+	+	....	+	+

Symbols have the following interpretations: (+), occasionally increased; +, moderately increased; ++, markedly increased; (—), occasionally decreased; —, moderately decreased; — —, markedly decreased, and — — —, very markedly decreased.

(table 2). It cannot be said, however, that the electrophoretic pattern is diagnostic in any cutaneous disease since similar changes occur in many unrelated diseases. The various changes in the electrophoretic pattern tend to be proportional to the severity of the disease and therefore may be slight, or even absent, in mild cases of a given disease. In some diseases the electrophoretic pattern varies with the stage or the duration of the disease. It is a basic rule that in acute inflammatory diseases

a decrease in albumin and an increase in the alpha globulins occurs, whereas in chronic granulomatous or fibrotic diseases an increase in gamma globulin is observed. Thus, several diseases, e.g., eczema, pemphigus, erythema nodosum and lymphogranuloma venereum, may show at first an increase in the alpha globulins and later an increase in gamma globulin.

The various protein fractions have different properties and functions. Therefore, a discussion of the electrophoretic patterns in various cutaneous diseases is best based on observation of the changes produced by these diseases in each of the electrophoretic fractions.

Albumin.—A significant increase in albumin above normal values does not occur. A decrease in albumin occurs when there is either impairment of albumin formation or excessive loss of albumin. Impairment of albumin formation in cutaneous diseases occurs either in association with dysfunction of the liver, which is the main site of albumin formation,[37] or in association with high fever or emaciation. Excessive loss of albumin in cutaneous diseases occurs in association with extensive bulla formation or oozing. In addition, one often finds a slight compensatory decrease in albumin in cutaneous diseases in which other protein components, especially the alpha or gamma globulins, are considerably increased.

Among cutaneous diseases, impairment of albumin formation due to dysfunction of the liver occurs in biliary xanthomatosis (biliary cirrhosis with xanthomatosis). Impairment of albumin formation due to high fever or emaciation occurs especially in pemphigus, acute systemic lupus erythematosus, dermatomyositis and lymphoma. Excessive loss of albumin due to bulla formation or oozing occurs in extensive eczema, burns, pemphigus and severe erythema multiforme. Although in diseases with bulla formation or oozing all protein components are lost in the exudate at approximately the same ratio as that in which they are present in the corresponding blood serum,[38] a low albumin level gradually develops in the blood plasma because albumin is regenerated much more slowly than are the globulin fractions.[39]

Of all cutaneous diseases investigated by us, pemphigus vulgaris acutus showed by far the lowest values for albumin. In six of the seven patients examined in the advanced stage of the disease the amount of albumin was less than 25 per cent of the total protein, or, expressed in absolute values, less than 1.5 Gm. per 100 ml. of serum. One case of severe acute dermatomyositis also showed considerable lowering of the albumin, to 28.9 per cent, or 1.18 Gm. per 100 ml. of serum. Albumin values of less than 2 Gm. per 100 ml. of serum were observed also in two patients with pemphigus foliaceus and in one patient each with generalized eczema, generalized psoriatic erythroderma, pemphigus vulgaris chronicus, pemphigus vegetans, erythema multiforme and acute systemic lupus erythematosus.

Alpha Globulins.—The alpha globulins are increased in diseases associated with high fever or with tissue destruction. Since the alpha globulins have a higher content of polysaccharide (hexose) than other globulins,[40] diseases with an increase

37. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20**:194, 1940.

38. Lever, footnotes 5 and 14.

39. Zeldis, L. J., and Alling, E. L.: Plasma Protein Metabolism: Electrophoretic Studies; Restoration of Circulating Proteins Following Acute Depletion by Plasmapheresis, J. Exper. Med. **81**:515, 1945.

40. Lever et. al.[1] Seibert et. al.[21b]

of the alpha globulins show an increase in the hexose content of the blood.[21b] Among cutaneous diseases a considerable increase in the alpha globulins may occur especially in pemphigus vulgaris acutus, pemphigus vegetans, extensive burns and dermatomyositis. A moderate increase may be found in extensive eczema, extensive psoriasis, pemphigus vulgaris chronicus, pemphigus foliaceus, severe erythema multiforme, erythema nodosum, leprosy, lymphogranuloma venereum and lymphoma.

Among the patients investigated by us, five of the eight patients with pemphigus vulgaris acutus and one patient each with pemphigus foliaceus, pemphigus vegetans and dermatomyositis showed an increase in the relative value of the alpha globulins to more than twice the normal relative amount, i.e., to a value greater than 30 per cent of the total protein. Moderate increases in the alpha globulins were frequently present in all diseases with extensive involvement of the skin. Values for alpha globulin in excess of 20 per cent were found in two of eight patients with eczema, four of eight patients with psoriasis, all eight patients with pemphigus vulgaris acutus, five of seven patients with pemphigus vulgaris chronicus, all four patients with pemphigus foliaceus, one of two patients with pemphigus vegetans, two of four patients with erythema multiforme, one patient with erythema nodosum, one of three patients with chronic discoid lupus erythematosus, one of seven patients with acute systemic lupus erythematosus, all three patients with dermatomyositis, four of eight patients with diffuse scleroderma and one of three patients with sarcoidosis. It is interesting that even the severe cases of acute systemic lupus erythematosus showed—in contrast to observations in dermatomyositis—either no or only a slight increase in the alpha globulins.

Beta-1 Globulin.—From a clinical point of view, the most important component of the beta-1 globulin is beta lipoprotein. Whereas neutral fat does not contribute to the electrophoretic pattern, cholesterol and phospholipids do because they are present in the serum largely, if not entirely, as lipoproteins. Excess cholesterol and phospholipids occur entirely as beta lipoprotein. Therefore, an increase in the beta-1 globulin occurs in diseases associated with an increase in the cholesterol and phospholipid content of the blood serum. A marked increase in the amount of beta-1 globulin occurs in primary familial xanthomatosis and in biliary cirrhosis with xanthomatosis, and a moderate increase in myxedema and in myxedema circumscriptum.

Among our patients both patients with biliary cirrhosis with xanthomatosis and three of the four patients with primary familial xanthomatosis showed appreciable elevation of the beta-1 globulin. The fourth patient with primary familial xanthomatosis showed a moderate elevation of the beta-1 globulin. One patient with myxedema circumscriptum had a slight elevation of the beta-1 globulin.

Beta-2 Globulin (Fibrinogen).—In serum the amount of beta-2 globulin is small, usually about 4 per cent. No significant quantitative changes in this fraction occur in cutaneous diseases. In plasma fibrinogen migrates as a beta-2 globulin and an increase in the size of the beta-2 peak is generally interpreted as an increase in the amount of fibrinogen. An increase in fibrinogen occurs especially in febrile diseases and in cases of extensive tissue destruction, i.e., under the same conditions under which the alpha globulins are increased.

In the majority of our patients serum rather than plasma was examined, and, therefore, only few data on the amount of fibrinogen are available. A marked increase in fibrinogen was observed in the one patient with pemphigus vulgaris acutus in whom plasma was examined. The beta-2 globulin in this patient was raised from a relative value of 8 per cent to a value of 18 per cent, that observation indicating an increase in fibrinogen from 4 per cent to 14 per cent. Moderate increases in the amount of fibrinogen, indicated by values for beta-2 above 10 per cent, were observed in one patient with eczema, one patient with psoriasis, two patients with pemphigus foliaceus and one patient with mycosis fungoides.

Gamma Globulin.—The amount of gamma globulin is increased in patients with prolonged allergic reactions, with chronic infections and with liver disease. The increase in gamma globulin in chronic infections is in part due to the formation of antibodies which migrate almost entirely as gamma globulin.[41]

Cutaneous diseases in which high gamma globulin values occur on the basis of a prolonged allergic reaction are extensive eczema, pemphigus vulgaris acutus, pemphigus vegetans, acute systemic lupus erythematosus and systemic scleroderma; moderate elevations on the basis of a prolonged allergic reaction occur in pemphigus vulgaris chronicus, pemphigus foliaceus, erythema multiforme, erythema nodosum, chronic discoid lupus erythematosus, chronic disseminate lupus erythematosus and circumscribed scleroderma. High gamma globulin values on the basis of chronic infection are found in erythema induratum, sarcoidosis, leprosy, lymphogranuloma venereum and yaws; moderate elevations on the basis of chronic infection occur in lupus vulgaris, syphilis and pinta. High gamma globulin values on the basis of liver disease occur in biliary cirrhosis with xanthomatosis. In addition, fairly high gamma globulin values occur in patients with extensive lymphoma.

Among our patients values of gamma globulin exceeding 20 per cent of the total protein were found in three of seven patients with extensive eczema, four of seven patients with advanced pemphigus vulgaris acutus, one of seven patients with pemphigus vulgaris chronicus, one of four patients with pemphigus foliaceus, one of two patients with pemphigus vegetans, six of seven patients with acute systemic lupus erythematosus, five of eight patients with diffuse scleroderma, one patient with erythema induratum, one of three patients with sarcoidosis and both patients with biliary xanthomatosis (after ether extraction).

It is of interest that our patients with generalized psoriatic erythroderma, even the two patients with associated rheumatoid arthritis, showed—in contrast to the patients with generalized eczematous erythroderma—no elevation of the gamma globulin. As far as dermatomyositis is concerned, Walker and Benditt [18] had found in four cases of dermatomyositis—in contrast to the observations in lupus erythematosus—no increase in the absolute values for gamma globulin. Of our three patients, two showed normal values for gamma globulin while in one patient the values for gamma globulin were, on two occasions, slightly elevated, relatively as well as absolutely. The fact remains, however, that the values for gamma globulin are distinctly lower in dermatomyositis than in acute systemic lupus erythematosus.

41. Tiselius, A., and Kabat, E. A.: An Electrophoretic Study of Immune Sera and Purified Antibody Preparations, J. Exper. Med. **69**:119, 1939. Enders, J. F.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: X. The Concentrations of Certain Antibodies in Globulin Fractions Derived From Human Blood Plasma, J. Clin. Invest. **23**:510, 1944.

SUMMARY

Significant changes in the electrophoretic pattern were observed in many diseases of the skin.

The electrophoretic patterns obtained in cutaneous diseases are of no diagnostic value. Rather, they reflect the patient's reaction to his disease. Thus, electrophoretic analysis contributes to the understanding of the effect that a given disease has on the patient.

In several patients the effect of treatment on the electrophoretic pattern was studied. In patients with severe pemphigus vulgaris and hypoalbuminemia intravenous infusions of human serum albumin produced a considerable increase in the amount of albumin in the blood serum. In patients with acute systemic lupus erythematosus and diffuse scleroderma injections of ACTH caused consistently a significant decrease in gamma globulin. Similarly, in one patient with sarcoidosis administration of massive doses of vitamin D resulted in a decrease in gamma globulin.

TREATMENT OF CHRONIC CUTANEOUS PROBLEMS WITH CALCIFEROL

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AS THE result of our stimulation by the fact that calciferol improved or cured the previously chronic resistant and progressive disease lupus vulgaris, the present study, for the sake of investigation, was done. This project was started in October 1948 and extended to December 1949. The material used was a highly potent calciferol [1] (vitamin D_2, 1,250 units per drop) in propylene glycol.

The amount of the drug used depended on the age of the patient and the individual reactions. The youngest was 2 years of age, and the oldest 72. The minimal dosage was 2 drops (2,500 units) three times a day, and the maximum was 40 drops (50,000 units) three times a day. The longest period of treatment was 14 months, during which time many of the patients received a minimum dose of 50,000 units daily. The dose of the drug was increased or decreased according to the observed improvement or lack of response on the part of the patient, so that eventually the daily dose was the minimal amount necessary to keep the patient improved, if he was responding to the drug. The fact that the supply of calciferol was limited and often unavailable for five to six weeks was both a hindrance and a help. As to the former, it prevented us from using the treatment in a larger number of diseases, data on which might have been included in this series. As the latter, it forced the minimal dosage necessary to help the patients and provided an indication of the rate of relapse.

DRUG REACTIONS

According to Pascher [2] and her group, toxic manifestations attributed to calciferol should be divided into two groups: (1) symptoms of toxicity and (2) chemical manifestations of toxicity. Under the former classification are nausea, vomiting, abdominal pain, loss of appetite, fatigue and weakness, frequency of urination, nocturia, thirst, loss of weight and joint pains; under the latter, albumi-

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Dr. Leon Goldman, Dr. H. Jerry Lavender and Dr. Alfred Weiner assisted in the preparation of this paper.

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1. The calciferol in propylene glycol was supplied by Winthrop-Stearns, Inc., Buffalo.

2. Pascher, F.; Silverberg, M. G.; Marks, I. E., and Markel, J.: Therapeutic Assays of the New York Skin and Cancer Unit, Post Graduate Medical School, New York University-Bellevue Medical Center: Assay II—Calciferol (D_2), J. Invest. Dermat. **13**:89-98 (Aug.) 1949.

nuria, hypercalcemia, alkaline phosphatasemia and increase in the blood urea nitrogen. Except in two patients no untoward reactions were noted. The reactions observed consisted in mild nausea and vomiting and an elevation of the blood urea nitrogen to 56 mg. per 100 cc. of blood. In both patients the manifestations were quickly controlled when use of the drug was stopped, and in neither did they return when administration of the drug was repeated at a lower maintenance dose.

LABORATORY STUDIES

The indicated laboratory studies were repeated examinations of the blood, urinalysis and blood calcium, phosphorus and urea nitrogen determinations. These repeated studies, for the most part, were made only on the General Hospital patients. All but three of the patients were seen in office practice. The three exceptions were studied carefully at the Cincinnati General Hospital on the dermatology service, and the indicated laboratory studies were made on these persons. Short abstracts of these cases are included in this paper. From time to time blood studies were made on certain of the office patients. Pascher and her group stated that hypercalcemia developed in 60 per cent of the persons examined at regular intervals. This rise in total serum calcium occurred as early as the second month in some cases and not until the tenth month in one case. It is interesting to note here that the average blood calcium level in this study was 11.6 mg. per 100 cc. This observation can readily be understood when we realize that the average daily dose for our patients was not as great as that for those treated by Pascher. An analysis of the results of treatment with calciferol therapy and some short case summaries follow.

ATOPIC DERMATITIS

Three patients who had long been sufferers from atopic dermatitis and who had been treated and re-treated on numerous occasions, both in and out of the Cincinnati General Hospital, with all types of therapy and with little improvement were the first to be treated. It was decided that they should be given the medication for at least three months and that if at the end of that time there had been no improvement this study would be abandoned. Incidentally, because of their response to treatment persons with other chronic skin diseases were included in this investigation.

Case 1.—D. S., 19 years old, was admitted to the Cincinnati General Hospital skin ward on July 22, 1948 for re-treatment of his severe atopic dermatitis. He had been in the same hospital on many occasions since he was 3 months of age; in fact, he had been in the hospital more than he had been out of it. He was sensitive to innumerable foods and also had bronchial asthma and bilateral cataracts. The latter had developed in 1946, and despite operative procedures the patient had become partially blind and was learning to read braille. During his numerous hospitalizations he had experienced only transient improvement. The patient was poorly developed and appeared about 14 years of age. His skin was erythematous, lichenified and scaling. The extremities were crusted, oozing and excoriated and were covered with scattered superimposed pustules.

On Oct. 11, 1948 treatment with calciferol, 50,000 units three times a day, was begun. During this therapy routine wet dressings with aluminum acetate (Burow's) solution and application of mild boric acid cream were continued. Although up to this time the patient had failed to improve on local therapy, by October 23 he had improved sufficiently to be discharged to a foster home. He continued on treatment with calciferol, 50,000 units three times a day, through February 1949, during which time his skin remained in excellent condition

though dry. At no time did he experience any relapse or toxic reactions. He is now employed for the first time in his life.

Laboratory Studies.—On July 23, 1948 the hemoglobin was 13 Gm.; red blood cells, 5,540,000, and white blood cells, 12,250, with 45 neutrophils, 35 eosinophils, 18 lymphocytes and 2 monocytes. Results of urinalysis were normal.

Determinations of blood calcium, phosphorus and urea nitrogen, in milligrams per 100 cc., were as follows:

	October 1948	November 1948	January 1949	February 1949
Blood calcium	11.3	12.5	12.0	11.6
Blood phosphorus	4.6	4.0	4.8	4.3
Blood urea nitrogen	10.6	11.3	9.1	10.0

In November 1948 the hemoglobin was 13.5 Gm.; red blood cells 5,400,000, and white blood cells, 8,500, with 50 neutrophils, 10 eosinophils, 38 lymphocytes and 2 monocytes.

The response of this patient to calciferol was extremely encouraging, particularly since, as stated above, his condition had been refractory to all previous types of therapy. His asthma did not respond to calciferol.

CASE 2.—A. W. was admitted to the Cincinnati General Hospital dermatology service Sept. 21, 1948 for the ninth time since 1939, when he had first been admitted for the treatment of his severe and extensive atopic dermatitis. Prior to that time he had been a faithful clinic patient since the age of 3 months. He also had hay fever and asthma. Physical examination showed a poorly developed white man appearing much older than his stated age. A generalized erythematous and scaling eruption was present, most pronounced on the face, ears, neck and extremities. This was associated with marked lichenification. The right eye had a cataract of 10 years' duration. Despite all types of previous treatment the patient had experienced very little relief or improvement. On Nov. 22, 1948 treatment was begun with calciferol in propylene glycol, 50,000 units three times a day. In eight days the skin showed definite improvement, and the patient was discharged on Dec. 2, 1948 on a maintenance dosage of 50,000 units of calciferol three times a day. His improvement continued until January 23, at which time he discontinued taking calciferol for three weeks. When he next appeared at the dermatology clinic it was noted that a definite relapse had occurred. Calciferol was again started, 50,000 units daily until March 22, 1949, when his skin again appeared clear except for residual lichenification. On subsequent examinations at the skin clinic his skin appeared clear, and he stated that he was working steadily for the first time since 1944. His asthma did not respond to treatment.

Laboratory Observations.—The hemogram and results of urinalysis were normal throughout the treatment. Blood calcium, phosphorus and urea nitrogen determinations, in milligrams per 100 cc., over a four month period were as follows:

	Oct. 25, 1948	Nov. 23, 1948	Dec. 22, 1948	Jan. 21, 1949
Blood calcium	11.1	11.8	11.9	11.8
Blood phosphorus	4.1	4.4	3.2	4.2
Blood urea nitrogen	11.0	11.0	12.0	11.1

This patient had a very gratifying result from treatment with calciferol and at no time experienced any toxic reactions.

CASE 3.—E. V., a 23 year old woman, was admitted to the Cincinnati General Hospital dermatology service on Dec. 23, 1948 with a history of having had atopic dermatitis since childhood. Since 1934 she had been hospitalized four times. On this admission, an exudative dermatitis was present on the face, extremities and body. The patient appeared to be well nourished but in acute discomfort. No cataract, asthma or hay fever was present in this case. The patient was immediately placed on treatment with 15 drops of calciferol three times a day and was discharged on Jan. 13, 1949, improved. She was again seen at the skin clinic in February, March and April, at which times her skin was still lichenified, but at no time had she experienced any exacerbations.

Laboratory Studies.—The hemogram and results of examination of the urine were normal throughout treatment. The blood calcium, phosphorus and urea nitrogen determinations, in milligrams per 100 cc., were as follows:

	Dec. 27, 1948	Jan. 15, 1949	Feb. 13, 1949
Blood calcium	9.60	9.58	13.30
Blood phosphorus	2.98	3.20	3.28
Blood urea nitrogen	11.00	10.80	11.20

The result in this patient was not as dramatic at that in the two previous patients, but there was improvement. She was the only patient of the three that at any time showed a rise in the blood calcium even though she experienced no symptoms of toxicity.

A summary of data concerning these three patients with severe atopic dermatitis should include the fact that during calciferol therapy concomitant local treatment was restricted to Burow's solution wet dressings, application of boric acid salve and colloid baths. This same type of therapy without calciferol had failed in the same three patients on many previous occasions.

This initial experience with calciferol therapy appeared to warrant its trial for office patients, and this was started in February 1949 and continued until December 1949. During this period 20 patients with atopic dermatitis were treated with calciferol, and, although at the time of examination or during the follow-up periods their condition was not severe enough for them to be hospitalized, a large percentage of these persons had severe cutaneous reactions and many had been hospitalized on

TABLE 1.—*Composite Average Blood Chemistry Determinations for Four Months*

Blood calcium	11.64 mg./100 cc.
Blood phosphorus	3.84 mg./100 cc.
Blood urea nitrogen	11.0 mg./100 cc.

numerous occasions in the past. Their age varied from 2 to 46 years, and a number of these patients had been under the care either of a general physician or of a specialist most of their lives and had been treated with all types of therapy.

After treatment with calciferol was instituted, a large percentage of these patients stated that they noted improvement in their skin during the first three weeks of treatment. There was diminution in the pruritus and a decrease in the erythema. The factor that appeared to be most striking was the decrease in the number of office visits that the individual person made as compared with the average number of office visits in the two or three years previous to calciferol therapy. This fact was further evidenced by the patients' own voluntary statements. For younger persons the initial dosage was 3 to 5 drops three times a day (3,750 to 6,250 units daily), and the amount was increased or decreased proportionately to the response of the patient. At no time were there any complaints of toxic reactions, and in this younger group blood chemistry studies were not done. In young adolescents and older patients, the dosage was usually 10 drops three times a day (12,500 units) and was often increased to 25 or 40 drops three times a day (32,000 to 50,000 units). In this group a few of the patients experienced mild toxic reactions and only occasional blood chemistry examinations were made. In the case of a nurse the blood urea nitrogen rose to 56 mg. per 100 cc. and she experienced nausea, but reduction of the dose reduced the blood urea nitrogen and stopped her symptoms. One patient was seen with an acute flare-up of her atopic dermatitis during her last trimester of pregnancy. In addition to bland therapy she was given

50,000 units of calciferol twice daily. Improvement was noted in three weeks, and the calciferol therapy was continued until after delivery. Mild albuminuria developed, necessitating the discontinuation of calciferol. The dermatitis again flared, and, despite the intermittent quality of the albuminuria, 50,000 units of calciferol was given daily. There were no toxic reactions, and the urine became normal. The patient continued to take calciferol for two more months, with improvement, and has not been seen since that time.

Because of the limited supply of this drug, only a few of the patients could be treated for periods longer than three months, and these took 15 drops of the drug daily as a maintenance dose for nine months. In the latter group there were a few relapses, and these were controlled by local and x-ray therapy.

Table 2 helps to give a fair analysis of these cases. Some of the patients did not give adequate information as to how many office visits they had made and used

TABLE 2.—*Analysis of Response of Atopic Dermatitis (Office Practice Patients) to Calciferol Therapy*

Patient	Duration of Disease, Years	No. of Office Visits During Year Before Treatment	No. of Office Visits After Treatment	Improvement	No. of Relapses	Failure
R. E.	16	Numerous	6	Yes	..	....
R. B.	2	Numerous	9	Yes	..	....
B. C.	14	Numerous	13	Yes	2	....
W. D.	27	Numerous	4	Yes	2	....
K. F.	23	Numerous	14	Yes	1	....
R. R.	18	Many	8	Yes	1	....
J. B.	6	Many	4	Yes	..	....
A. S.	6	Many	6	Yes	..	....
B. B.	14	Numerous	None	Yes	..	....
S. J.	5	Numerous	4	Yes	..	....
D. P.	6	Many	10	No	..	Yes
B. A.	34	Many	3	Yes	..	....
S. S.	8	Many	6	No	3	Yes
A. M.	7	Many	4	No	..	Yes
K. D.	2½	Unknown	7	Yes	..	....
A. S.	8	Patient had been hospitalized	..	Yes	2	....
J. C.	35	Unknown	9	Initially	2	Yes
M. R.	15	Many	8	Yes	..	....
R. H. B.	2	Numerous	4	Yes	..	....
L. S.	20	Numerous	4	Initially	1	?

the terms "numerous" and "many." In this group there were five who definitely failed to respond to treatment.

OTHER SKIN DISEASES

Chronic Eczematoid Dermatitis.—Thirteen patients with varying types of chronic eczematoid dermatitis were treated with calciferol. A number of these patients showed an initial improvement for three or four weeks and then experienced a relapse. None of them complained of any toxic symptoms while taking an average dose of 25 drops of calciferol daily. Again the limited supply of the drug precluded treatment for more than three months for any patient. Although many of these patients appeared to have initial improvement, this response did not continue long enough, so that about 65 per cent of these patients were listed as showing treatment failure. In the remaining 35 per cent there was a noticeable and sustained improvement on calciferol therapy. It appeared that some of these persons responsed better to x-ray therapy, to which they had been initially refractory, after they had taken calciferol for a number of weeks.

Psoriasis Vulgaris.—Nine patients with psoriasis vulgaris were treated with calciferol. Five of these patients had generalized psoriasis vulgaris, and four had focal psoriasis vulgaris. The average dosage of calciferol was 15 drops three times a day. In five of these patients there was improvement during the first three months of treatment; thereafter, relapse occurred in three of these five patients and further treatment with the drug was discontinued. Two of the patients not only improved under calciferol therapy but continued to improve after treatment was stopped. These last two patients are still being observed. Four patients failed to show any degree of response while under calciferol therapy. The patient in case 5 had his first attack of acute, generalized, guttate psoriasis vulgaris on Feb. 3, 1949 and was treated with calciferol, 15 drops three times a day. After two months of treatment the lesions began to disappear, and there was total clearance after four months of treatment. This patient had a rather dramatic response to the drug.

Although only a few cases of psoriasis vulgaris were treated with calciferol, it appears that in some patients clearance does take place while they are under calciferol therapy. Pascher [2] stated that in 27 cases of psoriasis vulgaris one patient was healed, four showed good improvement, three fair improvement and the remainder no improvement. In her series treatment was carried out for a minimum of four weeks and not longer than eight weeks. Kindler [3] treated 31 persons having psoriasis vulgaris, mostly women and children, with moderate doses of calciferol. Twelve of these patients responded with complete or almost complete recovery while on treatment with a daily dose of 50,000 to 100,000 units of calciferol for a period of several weeks to six months. Of the remaining 19 patients, seven improved.

Acne Conglobata.—A 17 year old girl with severe acne conglobata of the face and back was admitted to the Cincinnati General Hospital skin service on Oct. 12, 1949. She was placed on treatment with 50,000 units of calciferol twice daily and was discharged, improved, two weeks later. Treatment with calciferol was continued until December 1949, at which time the patient showed pronounced improvement. No other therapy was instituted during this period of observation.

Lupus Erythematosus.—Two patients with chronic discoid lupus erythematosus were treated with 20 drops of calciferol three times a day. After two months of therapy administration of the drug was discontinued inasmuch as these patients showed no improvement.

Granuloma Annulare.—A 6 year old patient with granuloma annulare of the instep was treated with 10 drops of calciferol three times a day for five months without any response to therapy. Hall [4] presented a case of granuloma annulare before the Los Angeles Dermatological Society and stated that dissemination of the lesions occurred five weeks after calciferol therapy was started—the dosage was 50,000 units three times a day. Maynard discussed this case and stated that he had been giving calciferol to patients with granuloma annulare for 15 years and believed it to be the only drug that cured this disease. Pascher and her group felt the drug was of no value in this particular disease and also noted dissemination of the lesions.

3. Kindler, T.: Psoriasis Treated with Calciferol, Brit. J. Dermat. & Syph. **61**:329-330 (Oct.) 1949.

4. Hall, A. F.: Granuloma Annulare, with Dissemination Following Calciferol Therapy, Arch. Dermat. & Syph. **61**:145-146 (Jan.) 1950.

Mycosis Fungoides.—A patient with mycosis fungoides was treated with calciferol, 25 drops three times a day for five weeks. Although the time was too short for any particular conclusions to be drawn, no response to treatment was noted.

CHEMISTRY AND ACTION OF THE DRUG

There seems to be some confusion in the minds of many physicians as to the true identity of calciferol, or vitamin D_2. Some believe it to be the same as irradiated ergosterol—it is not. Calciferol is manufactured by a process involving the irradiation of ergosterol and subsequent separation of the pure crystalline vitamin D_2 from other substances present. The manufacturers [5] state that crystalline vitamin D_2 has a constant potency of 40,000,000 U. S. P. units of vitamin D per gram, inasmuch as it is a chemically pure and uniform crystalline product, and as such is very stable. The designation "D_2" is employed to differentiate it from a compound formerly called "D_1," which consists of crystalline vitamin D_2 plus an inactive sterol known as lumisterol, which may be formed in the process of manufacture. Irradiated ergosterol, which contains not only D_2 but also other sterols, including lumisterol, is commonly referred to as vitamin D_1.

The action of calciferol has as yet not been definitely determined. Curtis [6] and his group have had a much wider experience than we have, and they state, "We feel

TABLE 3.—*Results of Treatment of Various Skin Diseases with Calciferol*

Diagnosis	Total No. of Cases	No. Showing Improvement	No. Showing Failure
Atopic dermatitis	20	15	5
Chronic eczematoid dermatitis	13	4	9
Psoriasis	9	5	4
Acne conglobata	1	1	0
Lupus erythematosus	2	0	2
Granuloma annulare	1	0	1
Mycosis fungoides	1	0	1

its main effects may be due to the removal of phosphorus from soft tissue and bone." Curtis [7] makes further comments in a discussion of Michelson's monograph on sarcoidosis, and I refer you to those statements. It is also of interest to make note of the fact that Charpy [8] insisted that "calciferol had to be administered in alcoholic solution according to a certain schedule in conjunction with calcium to obtain any results." This procedure appears unnecessary.

SUMMARY AND CONCLUSIONS

A 15 months' investigative study of the effects of high potency calciferol on several chronic cutaneous problems was made. The drug can be taken safely by all age groups for relatively long periods provided the daily dose is not excessive. The proper dose can be determined only by individual reactions. The signs and symp-

5. Personal communication to the authors from the manufacturers.

6. Curtis, A. C.; Taylor, H., Jr., and Grekin, R. H.: Sarcoidosis: Results of Treatment with Varying Amounts of Calciferol and Dihydrotachysterol, J. Invest. Dermat. **9**:131-150 (Sept.) 1947.

7. Michelson, H. E.: Sarcoidosis: Review and Appraisal, J. A. M. A. **136**:1034-1039 (April 17) 1948.

8. Charpy, cited by Cornbleet, T.: Calciferol and Streptomycin in Lupus Vulgaris, J. A. M. A. **138**:1150-1153 (Dec. 18) 1948.

toms of toxicity to calciferol have been reviewed, and only one patient manifested such toxicity in this study. Blood calcium, phosphorus and urea nitrogen studies were made on hospitalized patients and revealed no serious changes. Such studies were made sporadically on office patients and likewise revealed no abnormalities. This observation should not lull one into a false sense of security regarding the toxic manifestations of calciferol, inasmuch as the laboratory results do not always correspond to signs and symptoms. Pregnancy is no contraindication to calciferol therapy, although at this time there might be some difficulty in distinguishing intermittent albuminuria of pregnancy from that caused by calciferol therapy.

The favorable results attained in atopic dermatitis appear somewhat impressive. It is recommended that moderately large dosage be given for a minimum of three months before either favorable or unfavorable conclusions are made. If after three months of therapy there has been no response, the treatment should be abandoned. If, on the other hand, the response has been favorable, a moderately large daily maintenance dosage should be established. Practically all patients who have improved did so in the first three weeks of treatment. Mild local therapy should not be discontinued while the drug is being given, inasmuch as calciferol is not a specific and is far from a cure. The results in chronic eczematoid dermatitis were not as encouraging, but some of the patients responded. The results in psoriasis vulgaris were not conclusive, inasmuch as not a large enough group of patients was studied; however, clearance of lesions was noted in two patients. One patient with severe acne conglobata responded to treatment. Other patients with similar reactions have been placed on the drug, but the results were not available at the time of this report. Although only a few patients with chronic discoid lupus erythematosus, granuloma annulare and mycosis fungoides were treated, the drug appeared to be nonbeneficial in these cases.

The old adage of "make haste slowly" appears very apropos in this study, and because of somewhat promising results, particularly in atopic dermatitis, further experimentation with calciferol appears justified.

ADDENDUM.—One patient with widespread parapsoriasis of the xanthoerythroderma perstans type failed to respond to calciferol therapy. This patient received 50,000 units of the drug daily for three months.

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ABSTRACT OF DISCUSSION

DR. CLARENCE LIVINGOOD, Galveston, Texas: First of all, I wish to congratulate Dr. Goldberg on this fine presentation. All of us know that the accumulation of data such as this involves a tremendous amount of work, and often it is a thankless task.

Dr. Goldberg has stated that vitamin D_3 is an ineffective preparation for the treatment of a number of miscellaneous chronic dermatoses, including lupus erythematosus, chronic eczematoid dermatitis and psoriasis. On the other hand, he states with proper caution, that it appears to be an effective preparation in a fair percentage of cases of atopic dermatitis. To be exact, he has presented evidence which would indicate that 15 out of a series of 20 patients, while not cured, had satisfactory improvement and that in some instances persons who had been incapacitated for years were able to pursue a useful life. The five patients who did not improve included three children and two adults. An additional five patients who were included in the improved group had one or more relapses during the period of observation.

Dr. Goldberg did not have time to outline the course of all of these patients, but it is assumed that the relapses occurred when administration of the drug was discontinued, with a remission of symptoms and improvement of the condition when therapy was reinstituted. The results which are reported in this study would be more convincing if at least some of these patients had had periods of placebo treatment during the course of their treatment and observation. However, it is not easy to control a study such as this, and, in the final analysis, it would seem to me that the place of vitamin D_2 in our therapeutic armamentarium for the treatment of atopic dermatitis will depend on the results of accumulated experience of numerous dermatologists rather than those in the experience of any one person.

It is obvious that vitamin D_2 is not without toxic effects, and it is proper to question whether or not we are justified in using this preparation in the treatment of a disease which, although chronic and disabling, is essentially benign, especially with the understanding that long-continued therapy will be necessary if the desired results are to be obtained.

As Dr. Goldberg very properly emphasized, the calcium blood level and the urinary observations do not necessarily cover the field so far as possible toxic reactions are concerned. As he mentioned, no one knows and there is no way of measuring how many tubules of the kidney are damaged when this preparation is administered over a long period.

I am sure that Dr. Goldberg will agree that the use of calciferol in the treatment of atopic dermatitis is an experimental procedure. It should not be used by persons who do not have experience in the management of this disease. It would be most unfortunate if, for example, this treatment had newspaper publicity or lay publicity of any type. Indeed, I think that it would be most unfortunate if it were concluded by the general medical profession that here is a new hope for the treatment of "eczema," or atopic dermatitis. Until more data are accumulated, this experimental procedure should remain in the hands of those dermatologists who have an opportunity to carry out controlled experimental work.

Dr. Harry Templeton, Oakland, Calif.: Although we know very little about the pharmacodynamics of the vitamin D series, that is, vitamin D, D_2 and the tachysterols, we do know that they have a very powerful effect on the skin. We do not know whether they act on the calcium or the phosphorus metabolism, but their action lies somewhere in that area.

Shortly after Lever's work on treatment of pemphigus with dihydrotachysterol I was called to see a patient who had a generalized, typical case. Most of the skin was eroded. The patient could be described, in plain language, as a foul, stinking sticky mess. He was put on treatment with dihydrotachysterol, 3 cc. a day, and the dose gradually increased. I have never seen such a dramatic improvement in my experience in dermatology. Within two weeks, the skin was normal. Unfortunately, we did not know that we should have kept the patient on a maintenance dose. The treatment was stopped, and in a few months the pemphigus recurred. The patient did not respond to a second course of dihydrotachysterol, and he died.

After that experience we treated several persons with pemphigus with vitamin D. In two I know the condition to have been controlled over a period of several years. Another patient, who had a resistant pustular eruption of the palms and soles which had become generalized, requiring bed care at home, was placed on dihydrotachysterol therapy. When the dose reached the point where it produced anorexia and nausea, the eruption disappeared except for a few pustules on the palms and the soles, and the condition could be kept in remission (notice that I say "remission" rather than "cure") by means of this drug. She disappeared from observation but kept taking the drug. The next time I saw her, she was in the hospital with complete anuria, and it took heroic work on the part of the internist and the urologist to save her life. Despite this development, later on, when she had another relapse, she took the dihydrotachysterol again and could keep the disease under control with small doses.

I do not know the final word in regard to this type of therapy, but my impression is that this group of drugs has a powerful action on the skin. However, there is considerable danger in the use of them, and caution should be observed.

Dr. Merlin T. R. Maynard, San Jose, Calif.: I do not know whether I have had as large an experience with this particular drug as any of the other workers or whether I just think that I have. I started out in 1933 using it a great deal in my practice, then in the

form of viosterol (synthetic vitamin D U. S. P.) because calciferol was not available. When calciferol became available, I then began its use and have probably prescribed it 10 to 20 thousand times.

I want to say, about toxic reactions, that within the period I have mentioned I was at first delighted to have people come in and tell me how much better they felt and how good their appetites were; however, within a few days or a week they would complain that their appetites were gone, that they had headache and that they felt dizzy. At that time, I did not realize these symptoms were the signal of toxicity.

I have never observed a dangerous reaction to the use of calciferol, and I have used it in relatively large doses—however, not in the extremely large doses of 300,000 units or so that you hear of being used in psoriasis and other conditions. I have found that in psoriasis a much smaller dose is almost as effective.

The reactions that do occur are of a physiological nature. I have never seen any vicarious calcification. I have never observed any trouble with the arteries or with the joints. I have seen occasional calcinuria, but that can be watched for very easily by means of a Sulkowiesz test on the patient's urine. When a heavy dose is given, this test should be done often; it is a simple one that can be done in the office in a few seconds.

In many of my cases three months' period of treatment has been exceeded by many months. In some cases, I will stop administration of the drug for about two weeks, in order to get the level down a bit, and then go ahead with it.

I have had no success in the treatment of atopic dermatitis with this drug except in those cases in which lichenification is the dominant feature. Calciferol works very nicely in lichenoid dermatitis in that it has a limiting effect on the thickening.

I prescribed it in practically every case of psoriasis I saw up to five years ago; I have not used it much since then. In some cases the patient got well and stayed well, but in a great majority of them no improvement took place.

I have given it in the last few years in lupus erythematosus in the hope that it would do something, but so far I have seen no result that I could ascribe to the taking of calciferol. I probably will continue its use. I think it may have some long-term benefit, perhaps, but I have seen no satisfactory change in the lesions.

I also prescribed it routinely in granuloma annulare until I found some of the cases became disseminated and I decided it should not be used. In the other granulomas, such as lupus vulgaris, it can be used of course, as we know from the work of Charpey and others. Acne is a granulomatous disease. I think the benefit from calciferol in acne is probably due to the action on the granulomatous structure.

Dr. S. S. Bowen, Houston, Texas: I should like to report on the satisfactory use of calciferol in three cases of lupus miliaris disseminatus faciei, the small papular type of cutaneous tuberculosis frequently seen in Negro children.

Spectacular improvement within two weeks was noted in one case, with complete resolution in one month. The other two cases cleared within six weeks. The impressive fact to my associates and me was the excellent response to such comparatively small amounts of calciferol.

Our use of calciferol in extensive and previously resistant cases of granuloma annulare has been encouraging, with apparent cure after one month to six weeks of therapy.

Our routine of therapy has been to use 15 drops of calciferol three times daily. Larger doses may be given in the form of capsules, 50,000 units each. As much as 150,000 to 200,000 units may be given daily for several months. The addition of streptomycin, 1 Gm. daily, is said to improve the effect of calciferol in resistant cases of lupus vulgaris.

Dr. Lawrence C. Goldberg, Cincinnati: I deeply appreciate the discussion. I agree heartily with what Dr. Livingood stated. I, too, would feel very bad if there were some type of press publication indicating that this treatment was a cure. In no way do we believe that it will cure atopic dermatitis, but we did see some patients improve.

In answer to Dr. Maynard, the three patients we had in Cincinnati General Hospital all had exudative lesions; two had cataracts, one bilateral. They had never shown any improve-

ment at all previous to this treatment. The results were noted not only by myself but also by Dr. Dexter, who was the resident. I corroborate what she stated, although I examined the patients routinely.

Commenting on Dr. Templeton's discussion, I should like to reiterate the fact that dihydrotachysterol is a far more potent drug than calciferol, as has been indicated by the work of Dr. Curtis. He stated that, although the patients that had dihydrotachysterol improved, they had more toxic reactions than those who took calciferol. We believe that if one continues with 50,000 units of calciferol daily, he should not get into any difficulties, but we should like to reiterate the fact that the signs and symptoms of toxicity do not always go along with the laboratory observations. The patients may have toxicity, show nothing and yet have definite laboratory indications of the state.

In this particular study we did not follow any cases of tuberculoderma, unless you wish to call granuloma annulare, in which we had only negative results, a tuberculoderma. I agree that the treatment certainly has had dramatic effects in some of the other forms of cutaneous tuberculosis.

LICHEN SIMPLEX CHRONICUS (VIDAL) TREATED SUCCESSFULLY WITH PODOPHYLLIN

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NEW YORK

THE PURPOSE of this paper is to report the results of treatment with podophyllin (resin of podophyllum N. F.) in seven cases of circumscribed neurodermatitis. The patients had been treated previously with little or no response to orthodox measures, including roentgen therapy. Although the series of cases is small, the response was sufficiently impressive to recommend the use of podophyllin as a treatment worthy of further trial.

However, the impression should not be gained that the seven cases were consecutive. The patients were selected from a larger group treated since March 20, 1947 because they were observed for a sufficiently long period for careful evaluation of the results. A uniformly good result should not be expected.

The history, pharmacology and mode of action of podophyllin have already been thoroughly discussed by Sullivan [1] and Sullivan and King,[2] who need not be repeated here.

MATERIALS AND METHODS

Forms of Podophyllin.—The preparations of podophyllin used were as follows: (1) podophyllin, 0.25 to 10 per cent, in 10 parts of castor oil, 25 parts of aquaphor® (an oxycholesterol-petrolatum ointment base) and 65 parts of white petrolatum, and (2) podophyllin, 0.5 to 2 per cent, in 70 per cent alcohol.

Technic.—The technic here employed followed the general plan I previously described.[3] One inch (2.5 cm.) of skin beyond the edges of the lesions was coated with flexible collodion to protect the unaffected area from any inflammatory reaction to podophyllin ointment. The ointment was applied at weekly or twice weekly intervals; the site of application was then covered with wax paper and bandaged for 24 hours, and this procedure was followed by the application of a salve containing bismuth subgallate, 2; castor oil, 4, and white petrolatum sufficient to make 30 parts.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, Chairman, and the Skin and Cancer Unit of the New York University–Bellevue Medical Center.

1. Sullivan, M.: Podophyllotoxin, Arch. Dermat. & Syph. **60**:3 (July) 1949.

2. Sullivan, M., and King, L. S.: Effect of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:39-42 (July) 1947.

3. Garb, J.: Amyloidosis Cutis Treated with Resin of Podophyllum, Arch. Dermat. & Syph. **61**:520 (March) 1950; Amyloidosis Cutis, Lichenoid Type, Treated Successfully with Resin of Podophyllum, ibid. **62**:698 (Nov.) 1950.

REPORT OF CASES

CASE 1.—J. B., a man aged 27, complained on Oct. 28, 1947 of a severely pruritic eruption on his legs. The dermatosis was of 10 years' duration. On the middle two thirds of the extensor and outer surfaces of both legs were well defined lichenified patches. The histologic section showed the structure of lichen simplex chronicus. Low voltage x-ray treatments, 75 r each, were administered weekly for eight exposures to the left leg from Nov. 3 to Dec. 23, 1947. Antipruritic salves containing phenol and tripelennamine hydrochloride (pyribenzamine®) were applied with no noticeable regression of the lesions or alleviation of the itching.

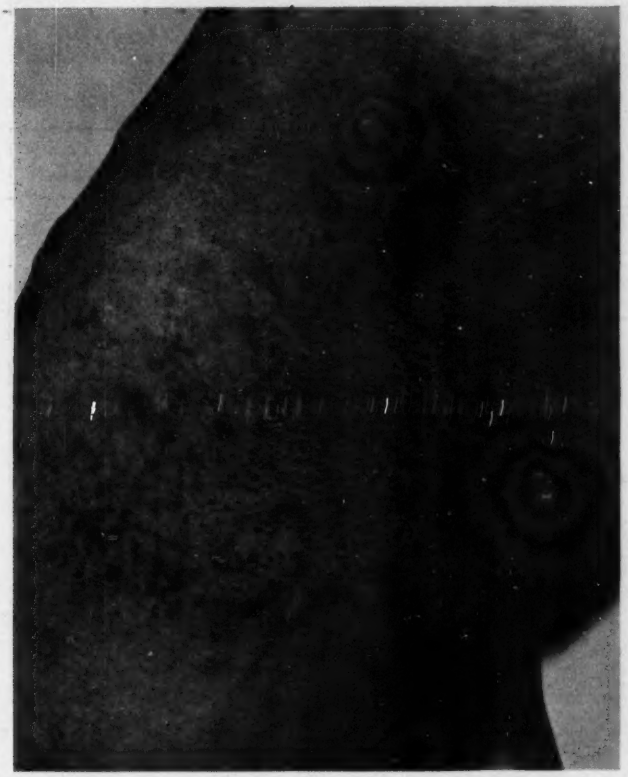

Fig. 1.—Photograph taken Aug. 10, 1948, showing the lichenified patch on the inner surface of the right thigh before treatment with x-rays.

On December 16, 10 per cent podophyllin ointment was applied to the right leg. A severe local inflammation followed, with "layers of the skin coming off in sheets." On January 13 the patient stated that the itching was slight and occurred only occasionally. The one application of the podophyllin ointment on the right leg proved vastly more effective than the eight x-ray exposures given to the left leg.

CASE 2.—A. T.,[4] a woman aged 39, on July 28, 1948 presented symmetrically distributed lesions on both thighs. The dermatosis was of 15 months' duration. The patient complained of moderately severe pruritus.

On the middle third of the inner surface of each thigh, more extensive on the right (figs. 1 and 2), was a large, uniformly erythematous and excoriated patch. The patches were sharply marginated and composed of closely aggregated, lichenified, somewhat shiny papules from the size of a pinhead to that of a split pea.

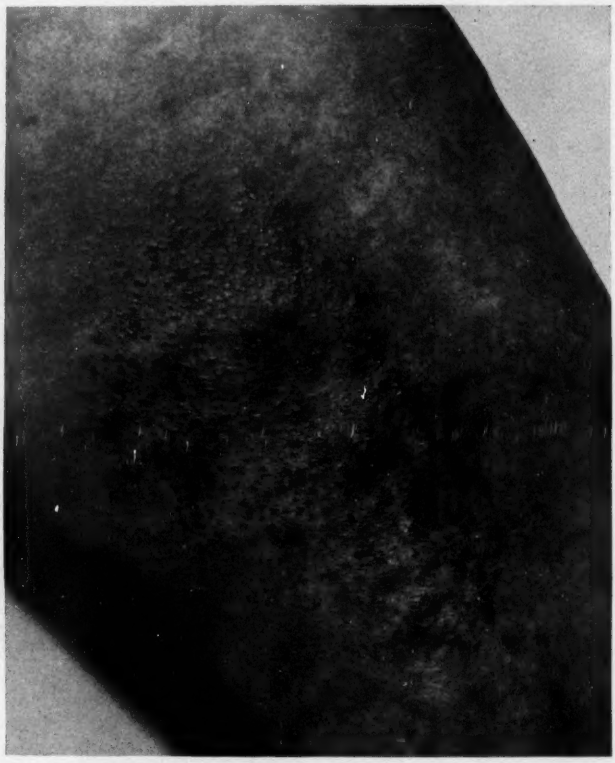

Fig. 2.—Photograph taken Aug. 10, 1948, showing the lichenified patch on the inner surface of the left thigh before treatment with podophyllin ointment.

X-ray exposures, 75 r each, were given to the right thigh beginning on August 3 and continuing once weekly, while the left thigh was treated simultaneously with weekly applications of increasing concentrations of podophyllin ointment (2.5 to 7.5 per cent).

After four treatments, the lesions on both thighs regressed considerably and the itching subsided almost entirely. The treatments were continued until the residual patches had undergone complete involution (figs. 3 and 4), the right thigh receiving the last of nine exposures on Oct. 14, 1948, for a total of 675 r.

4. Garb, J.: Neurodermatitis Treated with Resin of Podophyllum, Arch. Dermat. & Syph. **61**:690 (April) 1950.

On October 20 there was a mild recurrence on the upper part of the patch on the right thigh which had been treated with x-rays. The right thigh was then treated with 5 per cent podophyllin ointment on October 27 and November 23. The lesion completely regressed.

On Feb. 10, 1949 the patient again presented a recurrent patch on the right thigh. One per cent podophyllin ointment was applied then and 2.5 per cent on February 12. The patient was last seen on Nov. 15, 1949, when there was no evidence of any lesions.

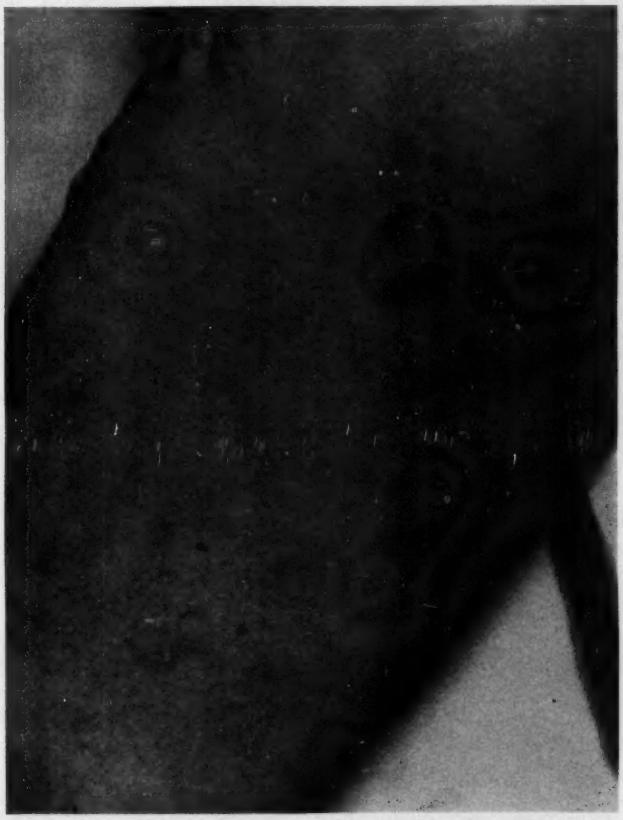

Fig. 3.—Photograph taken Sept. 28, 1948, showing the right thigh after nine x-ray exposures, 75 r each, still revealing some roughness in the area of the patch.

CASE 3.—M. D., a woman aged 50, on March 20, 1947 presented recurrent, lichenified, intensely pruritic patches on the back of the neck and on the extensor surface of the left elbow. The eruption was of several months' duration. Podophyllin ointment, from 1 to 5 per cent strength, was applied to the patches on March 20, 25 and 31, this treatment, resulting in rapid regression of the lesions. Because of a recurrence, 2.5 per cent podophyllin ointment was reapplied on May 28 and July 24, 1947. On Sept. 26, 1949 the patient consulted me about her ailing son. She stated that the podophyllin treatments had been very effective. Examination revealed no evidence of any lesions.

CASE 4.—The following is the history of a patient with severe lichen simplex chronicus treated with podophyllin by Dr. Paul Gross, who kindly allowed me to include his case in my series.

E. R., a woman aged 44, on Dec. 16, 1947 complained of an eruption on the hands, of five years' duration. She had previously been treated with topical medication and x-rays.

There was a sharply circumscribed, thickened, leathery and lichenified patch 3 inches (7.5 cm.) in diameter on the dorsal surface of each hand and a thickened, hyperkeratotic patch on the right thenar eminence. The latter patch responded favorably to application of phenindamine

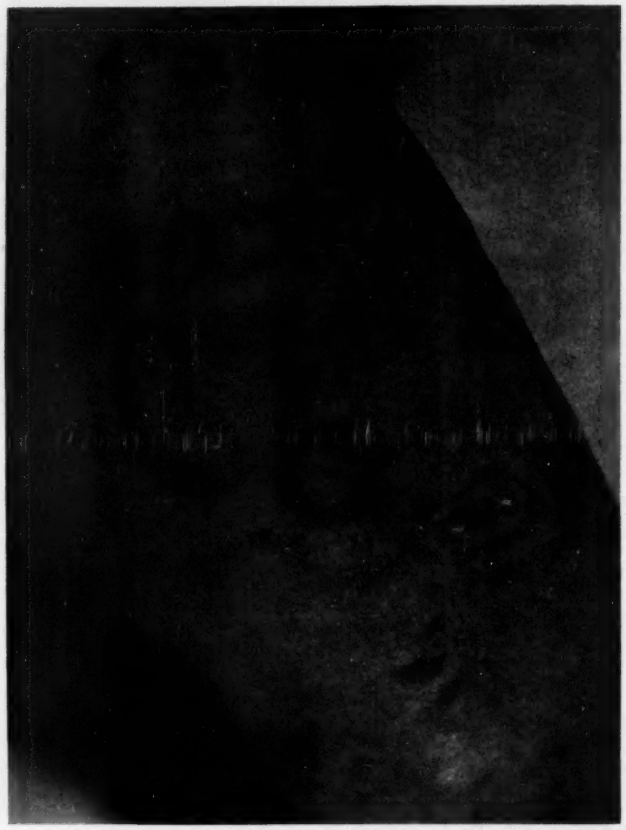

Fig. 4.—Photograph taken Sept. 28, 1948, showing the left thigh after treatment with podophyllin ointment during the same period that x-rays were used on the right thigh. Note that the surface is much smoother than that of the right thigh (fig. 3).

(thephorin®) ointment, but the lesions on the dorsal surface of the hands remained unchanged. On July 6, 1948, 2 per cent podophyllin ointment was prescribed, to be applied once daily. On July 13 there was no evidence of irritation on the hands and the itching was fully controlled by the use of the ointment. The patient did not return until Dec. 7, 1948. The patches on the dorsa of the hands had undergone complete involution. Only a superficial lichenified patch on the right thenar eminence was present.

CASE 5.—A. M., a girl aged 9, presented on May 28, 1949 a lichenified, pruritic, inflamed patch on the back of the neck. The dermatosis was of one year's duration. The patient had been having attacks of bronchitis as well. Three low voltage x-ray treatments had been administered to the neck by another dermatologist, without any improvement. On June 4, 1949 podophyllin ointment, 0.25 per cent, was applied to the back of the neck; applications were repeated twice weekly. On June 28, 1949, after seven applications, the patch had regressed almost entirely. The patient was advised to continue treatment with application of a bland ointment for the next three months, while she was in camp. Examination on Oct. 20, 1949 showed a small superficial patch in the left popliteal area and on the back of the neck. Podophyllin, 1 per cent in 70 per cent alcohol, was applied once a week at the office, and the aforementioned bismuth subgallate salve was prescribed to be used at home. On Feb. 1, 1950 only a trace of the lesions was present. The patient did not return until June 24, 1950, when there was no evidence of any lesions.

CASE 6.—V. G., a man aged 50, presented on Aug. 8, 1948 a hyperkeratotic, inelastic, rough, thickened, lichenified patch of 15 years' duration on the outer half of the dorsal surface of the left hand. He gave a history of having been treated in 1940 with 12 x-ray exposures, 75 r each, without any noticeable change. The patch regressed considerably in four weeks, after applications of 2.5 per cent podophyllin ointment twice weekly. There was a decided diminution in the degree of itching. Lichenified patches on the eyebrows and eyelids responded less rapidly to applications of 1 to 2 per cent of podophyllin in 70 per cent alcohol.

CASE 7.—E. W., a woman aged 45, presented on Oct. 24, 1947 four recurrent, well defined and very pruritic plaques on the insteps and outer surface of the right ankle, of about one year's duration. She was treated with weekly superficial x-ray exposures to a total of 2 skin units, 600 r. Podophyllin salve in concentrations of 2.5 to 5 per cent was applied on six occasions simultaneously with the x-ray treatments. Two lesions regressed almost completely, while two of the more infiltrated plaques responded poorly. On July 7, 1948, 25 per cent podophyllin salve was applied to the silver-dollar-sized plaque on the outer surface of the right ankle and 10 per cent salve to the lesion on the left instep. On July 12 the patient showed a severe inflammation of the ankle, which necessitated the use of wet dressings and an opiate.

COMMENT

Seven cases of lichen simplex chronicus treated with podophyllin, with good results in five, are herewith reported.

The advantages of podophyllin are as follows:

1. It appears to have been effective in reducing the lichenification.

2. Itching was quickly relieved.

3. The therapeutic benefits are apparently long lasting: In case 1 there was a striking result but the patient did not come for follow-up. In case 2 there was no recurrence after 13 months; in case 3, none after two years; in case 4, none after six months, and in case 5, none after five months. There apparently had been no recurrence since the last examinations in cases 2 and 3, as the patients would have communicated with me. In case 6 there was only a partial response and the patient in case 7 manifested a severe inflammation after application of 25 per cent podophyllin salve.

4. Podophyllin treatments may be repeated without injury to the tissues.

No untoward reactions occurred in the first six cases, but the possible complications of podophyllin therapy due to sensitization,[5] primary irritation from strong concentrations as in case 7 and corneal damage[6] due to accidental contact with podophyllin must be borne in mind.

5. Sullivan and King,[2] p. 34.

6. Rosner, R. S.: Corneal Insult from Podophyllin, Am. J. Ophth. **29**:1448 (Nov.) 1946.

It is advisable, therefore, to begin treatment with a mild podophyllin ointment (of a strength of 0.25 to 2.5 per cent according to the size, thickness and location of the lesions). Strengths up to 10 per cent may later on be used for resistant cases, since patients appear to acquire a tolerance to stronger concentrations.

When the possible complications are kept in mind and the aforementioned precautions are observed, podophyllin is recommended for the treatment of circumscribed neurodermatitis. Considering that this pruritic disease has been so troublesome to the dermatologist that even so severe a treatment as injections of alcohol has been suggested by Pels and Ellis,[7] this simple procedure offers great advantages.

A more rapid result may be expected if a mild podophyllin ointment (from 0.125 to 2 per cent according to the individual case) were to be prescribed to be used by the patient at home concurrently with the use of the ointment in the office. Results in a large series of patients treated with podophyllin ointment at the Treatment Unit of the Skin and Cancer Hospital will be reported later.

CONCLUSION

A report is herewith submitted of five out of seven cases of lichen simplex chronicus treated successfully with podophyllin ointment. The procedure is simple and effective. In five cases there was rapid regression of the lesions and allaying of the pruritus. The results compare favorably with those of x-ray therapy.

219 East Nineteenth Street (3).

7. Pels, I. R., and Ellis, F. A.: Circumscribed Neurodermatitis (Lichen Chronicus Simplex): Its Treatment by Injection of Alcohol, Arch. Dermat. & Syph. **54**:677 (Dec.) 1946.

USE OF MINERAL OIL IN THE MAINTENANCE OF CULTURES OF FUNGI PATHOGENIC FOR HUMANS

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AND
MARK A. GUTZKE, A.B.
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IN MANY laboratories the stock culture collections of human-pathogenic fungi are maintained in a viable state by storage either at room temperature or in a cold room. To insure survival of the cultures, frequent transfers are required, and with large collections this duty is an arduous one.

When maintained at room temperature, cotton-plugged cultures become dehydrated in a month or two and must be subcultured six or more times a year. At cold storage temperatures of 5 to 10 C. the transfer interval may be lengthened to three or four months. However, some of the fungi of medical importance (Microsporum audouini, Epidermophyton floccosum and Trichophyton schoenleini) do not survive such low temperatures and must be stored separately at room temperature.

In recent years several workers have investigated other methods of preserving fungi in a viable state for long periods. Raper and Alexander [1] successfully applied the process of lyophilization to a wide variety of fungi. Unfortunately, most anthropophilic fungi do not survive the severe conditions of freezing and drying used in that method. Buell and Weston,[2] following the example set by Sherf,[3] adopted another bacteriological procedure in which very favorable results were obtained by using mineral oil as a preservative. Although they had not tested any human-pathogenic fungi, it was reported that Page (Buell and Weston [2]) had successfully maintained cultures of Microsporum, Phialophora and Trichophyton under oil for nine months. A study therefore was undertaken by this laboratory to ascertain whether the same simple procedure could be applied to a wide variety of fungi pathogenic to man. Complete details of this method and a review of pertinent literature will be found in the paper by Buell and Weston.

Beginning in the fall of 1948, all fungi in the laboratory's culture collection as well as those subsequently added were subcultured on fresh slants of Sabouraud's dextrose agar. After the fungi had attained a colony size of approximately 1 cm.

From the Laboratory Services, Communicable Disease Center, Public Health Service, Federal Security Agency.

1. Raper, K. B., and Alexander, D. F.: Preservation of Molds by the Lyophil Process, Mycologia **37**:499-525, 1945.

2. Buell, C. B., and Weston, W. H.: Application of the Mineral Oil Conservation Method to Maintaining Collections of Fungous Cultures, Am. J. Bot. **34**:555-561, 1947.

3. Sherf, A. F.: A Method for Maintaining Phytomonas Sepedonica in Culture for Long Periods Without Transfer, Phytopathology **33**:330-332, 1943.

in diameter at room temperature, heavy mineral oil (autoclaved 30 minutes at 15 pounds [7 Kg.] pressure) was added in quantities sufficient to cover completely both the fungus growth and the surface of the agar slope. The tubes then were stored on sloping racks in a cabinet at room temperature. This temperature varied from 11 to 40 C. However, after removal of the tubes to an air-conditioned lab-

Viability of Human-Pathogenic Fungi After Storage Under Mineral Oil

Genera and Species	Number of Strains	Period of Viability to August 1950, Months
Allescheria		
boydii	10	21
Aspergillus		
fumigatus	3	20
Blastomyces		
brasiliensis	3	21
dermatitidis	6	20
Candida		
albicans	9	21
guilliermondi *	2	9
parapsilosis (parakrusei) *	4	11
stellatoidea *	5	19
tropicalis *	6	21
Cladosporium		
wernecki	2	20
Coccidioides		
immitis	3	21
Cryptococcus		
neoformans	14	21
Epidermophyton		
floccosum	8	21
Histoplasma		
capsulatum	7	20
Microsporum		
audouini	6	19
canis	12	19
gypseum	5	19
Monosporium		
apiospermum (See A. boydii)	..	..
Nocardia		
asteroides	6	21
mexicanus	4	19
Phialophora		
compactum	2	22
pedrosoi	14	21
verrucosa	7	20
Sporotrichum		
schenckii	9	21
Trichophyton		
concentricum	5	21
equinum	3	19
faviforme	14	21
ferrugineum	5	19
megnini	8	20
mentagrophytes	38	22
rubrum	13	21
schoenleini	9	19
tonsurans	10	14
violaceum	10	22
Trichosporon		
beigelii	2	14

* Rarely, if ever, pathogenic.

oratory in September 1949, the storage temperature was maintained at approximately 20 to 25 C. throughout the year. These oiled cultures were examined at regular intervals and their viability checked by removal of a small portion of the colony from beneath the oil and subculture of it on fresh tubes of Sabouraud's dextrose agar.

All the fungi placed under oil are still viable. The species tested and the length of time each has been so treated are recorded in the accompanying table.

It will be noted that Candida stellatoidea, E. floccosum, M. audouini and T. schoenleini are still viable after storage under oil for 19 to 21 months. These are the species that do not survive cold storage and which hitherto had to be held at room temperature and subcultured at monthly intervals.

Contrary to the findings of Page (in Buell and Weston [2]), oil storage did not prevent pleomorphic changes. Several strains of E. floccosum, which were non-pleomorphic when placed under oil, lost their original powdery, olive green form and became white and cottony and nonsporulating. Colony changes also were noted in cultures of Trichophyton mentagrophytes and Trichophyton tonsurans. No attempts were made to determine whether physiological changes other than those detectable by gross visual examination might have occurred.

The results obtained by storage under mineral oil of 264 strains of fungi representing 15 genera and 34 species have been so encouraging that we recommend this procedure as a method of choice to preserve human-pathogenic fungi in the viable state.

EFFECT OF ROENTGEN RAYS ON MICROSPORUM CANIS

An in Vitro Study

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FREEPORT, N. Y.

THE PRESENCE or absence of multichambered, spindle-shaped macroconidia or fuseaux has been considered one the foremost characteristic features aiding in the differentiation of the zoophilic and anthropophilic species of the genus Microsporum. There are, however, observations on record which tend to show that presence or absence of these structures under certain circumstances does not constitute the final basis for judgment. Benedek [1] found that Microsporum audouini formed fuseaux in the presence of a certain bacillus which he described and classified as Bacillus weidmaniensis. Hazen [2] saw increase in fuseaux production in M. audouini on the addition of yeast extract to the medium. Loewenthal [3] described a strain of Microsporum canis which lacked spindles in the primary colony and in some of its descendants, and he raised the question of whether or not there existed a relation between the species closer than had been generally accepted. The belief was expressed that further progress in the elucidation of this problem could be made by studying the effect of various agents, including x-rays, on the variability of the genus.

The literature on the effect of x-rays on fungi in general was summarized by Duggar [4] in 1936. In 1950 Backus [5] presented a résumé on the occurrence and induction of mutation in fungi by various agents, including x-rays. The facts of interest for the present study are that fungi in general are rather insensitive to x-rays but that large doses have a lethal effect. Various degrees of injuries may be produced, according to the dose administered and the type of fungus treated. The production of mutants by x-rays did not assume major proportions until 1945, when Sansome, Demerec and Hollaender,[6] working with Neurospora crassa, correlated the rate of mutation with dosage and intensity of radiation.

From the Long Island College Hospital and the Department of Dermatology and Syphilology, State University Medical Center at New York City, College of Medicine.

1. Benedek, T.: Unilateral Stimulation of Microsporum Audouini by a New Species of Bacillus, Mycologia **35**:222, 1943.

2. Hazen, F. L.: Microsporum Audouini: The Effect of Yeast Extract, Thiamine, Pyridoxine and Bacillus Weidmaniensis on the Colony Characteristics of Macroconidia Formation, Mycologia **39**:200, 1947.

3. Loewenthal, K.: Fuseaux Formation of the Genus Microsporum, Arch. Dermat. & Syph. **61**:455 (March) 1950.

4. Duggar, B. M.: Biological Effects of Radiation: Mechanism and Measurement of Radiation Applications in Biology, Photochemical Reactions, Effects of Radiant Energy on Organisms and Organic Products, New York, McGraw-Hill Book Company, Inc., 1936.

5. Backus, E. J.: The Occurrence and Induction of Mutations in the Fungi, Tr. New York Acad. Sc. **12**:270, 1950.

6. Sansome, E. R.; Demerec, M., and Hollaender, A.: Quantitative Irradiation Experiments with Neurospora Crassa: I. Experiments with X-Rays, Am. J. Bot. **32**: 218, 1945.

The present study proposes to investigate as a first step the effect, if any, of a moderate dose of x-rays on the faculty of fuseaux formation of M. canis in vitro. A single exposure to 300 r unfiltered was chosen, since it approximates the dose generally used for epilation of certain Microsporum infections of the scalp. Quantitative studies were not intended.

MATERIALS AND METHOD

Two freshly isolated strains of M. canis were used. One with inconstant and weak fuseaux production was the subject of experiment 1; another, with the capacity to form abundant fuseaux, was employed for experiments 2 through 5. The medium was freshly prepared dextrose-peptone agar (Difco) slanted in test tubes. For each experiment four colonies were prepared. Two of them were irradiated through the wall of the test tube; two remained untreated, serving as controls. The irradiation took place the day of inoculation in experiments 1, 4 and 5. In experiment 2 the irradiation was done seven days, and in experiment 3, 14 days, after inoculation. The dose in each experiment was 300 r unfiltered. The additional data in experiments 1 through 3 were 80 kv., 5 ma., 20 cm. distance, 188 r per minute, Picker Zephyr, two valve tube rectification, oil flow tube. In experiments 4 and 5 the data were 85 kv., 5 ma., 20 cm. distance, 156 r per minute, Bracke-Seib Dermatron, two valve tube rectification, Eureka tube type 13—. The filtration value of the walls of the test tubes was not known. Plantings and replantings from the irradiated colonies and their respective controls were performed at varying intervals and frequencies. The respective data are to be found under the heading of each experiment. The number of slants prepared in each instance and the time intervals were identical for the test and respective control groups. The colonies were kept at room temperature and examined for macroscopic and microscopic changes at weekly intervals for at least three weeks. Deviations from this rule are noted below. Special attention was given to the number and structure of the fuseaux. To facilitate identification of the colonies, the irradiated colonies and their respective controls were also referred to as mother colonies or as colonies of the first generation, their immediate descendants as colonies of the second generation and so forth, in proper chronologic order.

EXPERIMENTS

EXPERIMENT 1.—Five transplants from the mother colonies were made at weekly intervals starting one week after irradiation. A sixth, and last, planting was done two weeks later. The mother colonies were observed for 35 days and the daughter colonies for 21 days each.

Results.—The untreated control colony of the first generation revealed single fuseaux only. Among six plantings, one showed many spindles, two others revealed a few and the rest were negative for fuseaux. No fuseaux were present in the irradiated mother colonies. Fuseaux production was resumed in most of their descendants. As a matter of fact, it seemed to be more vigorous and more regular in the plantings derived from the irradiated colonies than in those from the untreated colonies. No pathologic forms of fuseaux were observed.

COMMENT.—It is open to question whether or not cessation of fuseaux formation in the irradiated colonies or intensified resumption in the test colonies of the second generation was a result of the treatment, since fuseaux formation was erratic also in the control group.

EXPERIMENT 2.—Seven days after irradiation eight plantings were made from each of the mother colonies. Then four additional and successive generations of colonies were prepared at intervals of from three to five weeks. For these generations only a limited, variable number of colonies was used. Their selection was based on the display of certain changes to be described below. The mother colonies were observed for 63 days and each generation of descendants for at least 21 days.

Results.—No macroscopic and microscopic changes were seen in the irradiated colonies. In the five subsequent generations of the test group pathologic macroconidia were detected (figs. 1 and 2). These occurred most often in close association with fuseaux of normal appearance, but they were generally smaller. The distorted forms occurred about four times as frequently as the normal spindles. Although they assumed a variety of shapes, most of them had retained transverse septums, but the number of compartments was reduced. Some of the fuseaux were bent at various angles; in some the spindle shape was entirely lost. Swollen compartments alternated with contracted ones. Some fuseaux developed a round shape and consisted of two or three divisions only. The center compartment of the latter was globoid, while the two terminal compartments were reduced to short tail-like appendages. The total number of fuseaux, normal and distorted alike, gradually decreased to such an extent that with a single exception no fuseaux were found in the sixth generation. This exception was a group of normal spindles detected once in one of the colonies.

In this experiment also gross changes were observed. From the third generation of the test group on, and with increasing intensity in the subsequent generations, a heavy white fluffy aerial mycelium developed.

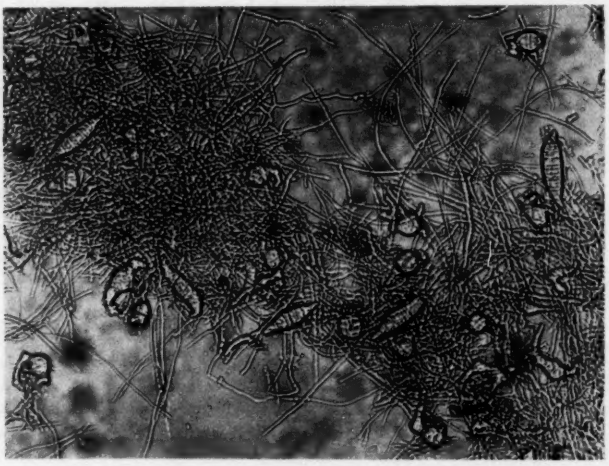

Fig. 1.—Distorted macroconidia occurring in association with fuseaux of normal appearance. This type of distortion was observed in experiments 2 and 3 (low power magnification).

The nontreated mother colonies with their five successive generations showed normal and abundant fuseaux. The colonies remained flat and felty and developed a yellowish brown pigment.

COMMENT.—While the mother colonies, irradiated and untreated alike, failed to show macroscopic and microscopic differences, distinctive features appeared in their respective descendants. The descendants of the former acquired the gross appearance commonly associated with pleomorphic degeneration, while the control colonies retained the characteristics of M. canis. In the descendants of the irradiated colonies, along with normal fuseaux, numerous bizarrely distorted macroconidia became visible, and the total number of fuseaux, normal and distorted alike, was gradually reduced to zero. That the disappearance was not complete and constituted possibly a reversible process seemed to be indicated by the detection of normal spindles in one colony of the sixth generation.

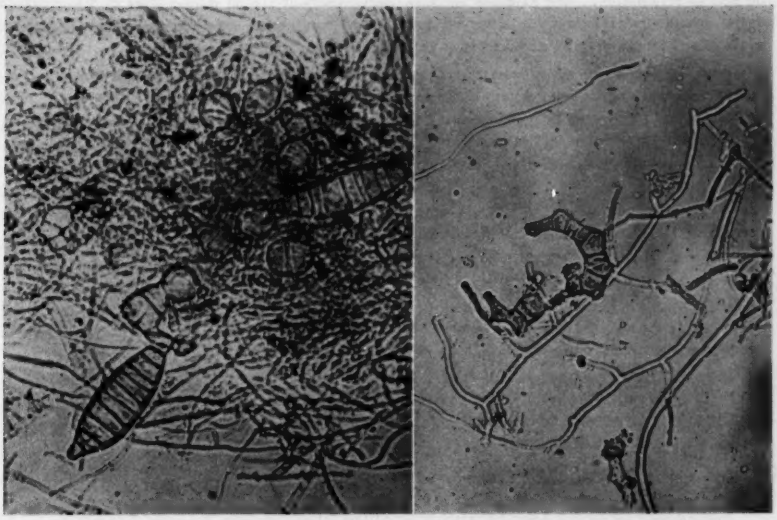

Fig. 2.—Grotesquely distorted fuseaux (high power magnification). Note that septums are retained.

EXPERIMENT 3.—Eight transplantations from the mother colonies were made one week after the day of irradiation. The primary colonies were observed for 35 days. Five of the colonies of the second generation were observed for 28 days, and three, for reasons to be explained below, were retransplanted and kept for an additional 55 days.

Results.—There was no gross or microscopic difference between the irradiated and the control colonies of the first generation. Both revealed abundant fuseaux of normal appearance. Five of the colonies of the second generation of the test group showed abundant spindles throughout an observation period of 28 days. Three other colonies were less constant, and toward the end of the prolonged observation period of three months their mycelium consisted of structureless masses with very few hyphae and without fuseaux. Only once, in one of the latter colonies, was a moderate number of distorted and normal spindles detected. The distorted fuseaux resembled those described as occurring in experiment 2. The faculty of fuseaux production was restored in half the colonies of the third generation, but the amorphous masses remained in almost all its colonies.

The number of fuseaux in the control colonies was not constant; in some the spindles were absent, but as a whole fuseaux formation was more regular in the control than in the test colonies. Structureless masses as well as distorted fuseaux were absent.

Three weeks after transplantation the test colonies of the third generation developed a heavy furry aerial mycelium. The control colonies, with one exception, formed a rapidly growing flat grooved mat with little aerial mycelium. The difference in appearance became more pronounced with increasing age of the colonies.

COMMENT.—Of special interest were the following findings in this test group: (*1*) the appearance of a disorganized mycelium in the second and third generation, (*2*) the detection of distorted fuseaux, (*3*) the disappearance of fuseaux from the second generation, (*4*) their reappearance in the third generation and (*5*) the development of a heavy white pleomorphic mycelium. While the control colonies of the second and third generation were inconstant as to quantity of fuseaux, distorted spindles and disorganized mycelium were absent. The gross cultural characteristics were those commonly seen in M. canis.

EXPERIMENT 4.—Plantings from the first generation were made at weekly intervals for four successive weeks starting one week after irradiation (second generation). Each of the colonies of the second generation was retransplanted once (third generation). At a later date, however, two of the colonies of the second generation were retransplanted a second time (third generation). One of the latter colonies having shown changes described below was transplanted again (fourth generation). The observation periods for the various colonies ranged between 28 and 63 days.

Results.—There was no gross or microscopic difference between the irradiated and the control colonies of the first generation. In seven out of eight colonies of the second test generation fuseaux were detected which differed from spindles of normal appearance and also from the distorted fuseaux of experiment 2. The most conspicuous changes were irregularity in size and shape, bending and fragmentation. The fragmented particles consisted of from one to four compartments with one blunt and one tapering end, or with two tapering ends, or with two blunt ends (fig. 3). Some of these structures resembled chlamydospores. The distorted fuseaux occurred either alone, replacing normal fuseaux, or more often in conjunction with the latter. Their number varied in the different colonies and also in various slides prepared from the same colony. There was an increasing difficulty in detection of fuseaux, normal and distorted alike, with increasing age of the test colonies of the second generation. Distorted spindles were still visible in the initial stage of some colonies of the third generation, but finally they disappeared, with one exception. The rest of the third test generation showed either normal fuseaux or none.

The exception mentioned above occurred in a colony which differed from the rest in gross appearance. It consisted of a flat, felty to powdery cinnamon brown mat with a narrow white fluffy fringe. On microscopic examination the fringe was observed to be made up almost

exclusively of hyphae with only single fuseaux, most of them normal in appearance. The mat contained abundant fuseaux, most of them fragmented or distorted. It was tried to segregate the fringe from the center by transplantation. The colonies derived from the center again showed a cinnamon brown felty mat with a peripheral fluffy border (fig. 4), while the colonies derived from the fringe showed a white, fluffy growth. Both exhibited an equal amount of

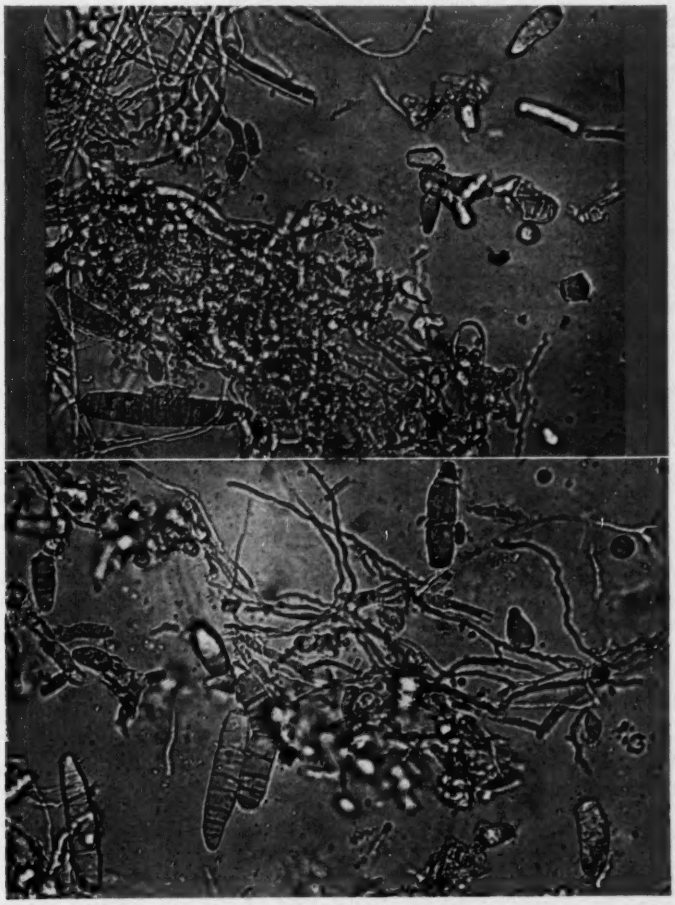

Fig. 3.—Fuseaux degradation as observed in experiments 4 and 5. The fuseaux are bent or fragmented into particles of various sizes and shapes. Most particles retain their septums. Some resemble chlamydospores (high power magnification).

canary yellow back pigment. The differences in the microscopic structure tended to disappear. Both contained from many to numerous distorted spindles, either alone or with a minority of normal fuseaux.

In the control group of the second generation a scarcity of fuseaux became more pronounced with increasing age of the colonies. The majority of the controls of the third generation became negative for fuseaux; the remainder showed from many to abundant fuseaux. An occasional distorted or fragmented spindle was detected.

COMMENT.—Of special interest are the occasional, though rare, detection of distorted fuseaux in the control group, the occurrence of numerous distorted or fragmented spindles in the second test generation and the appearance of a variant in the third test generation. The latter tended to retain its distinctive features in the following generation and continued producing distorted fuseaux although most of the colonies of the third generation had stopped doing so. The formation of normal fuseaux was erratic in both the test and the control group.

Fig. 4.—Transplant from the center of the variant colony of experiment 4. The colony retains, to a great extent, the characteristics of its ancestor, namely, the flat, felty, cinnamon brown central mat and a white, fluffy fringe toward the periphery.

EXPERIMENT 5.—The mother colonies were left undisturbed for a period of three months. Then two plantings were made which were followed, 20 days later, by two others. One of the former two plantings was retransplanted.

Results.—The primary test and control colonies did not reveal any difference in form, size, shape or pigmentation. Both contained normal fuseaux in amounts varying from moderate to abundant. In the second and third generation of the test group many distorted fuseaux were present, structurally identical with those in experiment 4 and occurring always in association with about equal numbers of normal spindles. Once, in one of the control colonies of the second generation, a few distorted forms were detected.

COMMENT.—The results resemble those obtained in the previous experiment. Of special interest is the fact that the treated mother colony, left undisturbed for three months subsequent to irradiation, remained undistinguishable, macroscopically

and microscopically, from the untreated mother colony. Structural changes occurred in the descendant test colonies. The changes were identical with those observed in experiment 4. As in that experiment, occasional distorted fuseaux were seen also in the test group.

COMMENT

A review of the results of the five experiments reveals the absence of any demonstrable macroscopic and microscopic effect of 300 r of unfiltered x-rays on the irradiated colonies themselves. This was particularly impressive in the fifth experiment, where the colonies were left untouched for three months. Changes occurring subsequent to irradiation could be demonstrated in the descendant colonies only. Although the changes in the various experiments differed in qualitative and quantitative aspects, a feature common to all but the first was a degradation of the fuseaux production. In the third experiment deteriorated fuseaux could be detected in relatively small numbers only. This was possibly a result of cessation of fuseaux production as a whole in conjunction with disorganization of the entire mycelium. The structural aberrations of the fuseaux in experiments 2 and 3 differed from those in experiments 4 and 5. Whether or not a specific significance must be attached to this variance in appearance cannot be decided. The degradation of the fuseaux was most often associated with a reduction of their total number, sometimes even to zero. In general, however, too great significance could not be attached to quantitative changes since the controls in many instances were also irregular and inconstant in this respect. For the same reason the result of the first experiment must be considered inconclusive. The observation that the deterioration of fuseaux formation was transmissible by way of transplantations through generations of colonies suggests a hereditary mechanism. The reoccurrence of normal fuseaux in the third generation of experiment 3 and in the sixth generation of experiment 2 appears to indicate that at least a partial recovery of the lost faculty was possible. The disorganized mycelial masses of the third experiment could not be identified as hyphae or fuseaux. This type of deterioration, occurring in two successive generations, was observed in that experiment only. It is noteworthy that, in spite of the great extent of disorganization, normal fuseaux were present after almost complete absence in one generation. In experiments 2 and 3 gross cultural changes occurred that were suggestive of pleomorphic degeneration. This term is being used with due reserve, for it represents a phase in the evolution of a fungus which is difficult to define. This difficulty was reflected in both instances in the fact that although the colonies presented the gross earmarks of pleomorphism occasional normal spindles were identified. Pleomorphic changes in M. canis are known to occur at a relatively early date. In these instances the onset was apparently accelerated subsequent to irradiation of the mother colonies. The observation of a variant in experiment 4 was a single occurrence among more than 300 plantings performed in these experiments. The variant, with its cinnamon brown powdery to felty mat and its abrupt fluffy white peripheral fringe, resembled M. gypseum. Though this variant occurred in the test group the conclusion that it was the result of the treatment cannot be based on this single event. The occasional detection of distorted spindles in the controls of experiments 4 and 5 seems to throw light on the mechanism underlying some of the changes observed in the test groups. It suggests that biologic deterioration, as evidenced by faulty fuseaux formation, may

occur spontaneously in an aging strain, the vitality of which has been further impaired by repeated subculturing and by growing on an artificial medium for a long period. This biologic downward trend apparently was intensified and accelerated subsequent to administration of 300 r of unfiltered x-rays.

Those data reveal a variety of responses on administration of the same dose. A few factors which may have contributed to this lack of uniform results are as follows: The experimental settings were not identical, although similar conditions were established in some; e. g., the settings in the fourth and fifth experiment were similar. Furthermore, two different strains with different biologic potentialities were employed, one in experiment 1 and the other in experiments 2 through 5. This resemblance in the experimental conditions is reflected in the results, since the findings in experiments 4 and 5 are related and the findings in experiments 2 through 5 as a whole differ from the findings in experiment 1. Characteristically variable and nonidentical factors prevailed, specifically (1) increasing age of the second strain as the experiments progressed, (2) varying time intervals between inoculation and irradiation on the one hand and between irradiation and planting of the daughter colonies on the other, (3) varying intervals between transplantations as well as varying frequencies of transplantations, (4) different observation period and (5) different physical factors pertaining to the x-rays administered. Even if standard conditions had been established the result of one experiment could not be easily duplicated, since some factors are hard to control: e. g., humidity of the air, the temperature or the fact that various particles of the transplanted material possess different biologic potentialities even if taken from a monospore culture. However, as indicated in the introduction, no quantitative studies were intended, and the present investigation must be looked at as a tentative step in the direction of a relatively unexplored field.

SUMMARY AND CONCLUSIONS

Colonies of M. canis growing on dextrose-peptone agar received one exposure of 300 r of unfiltered x-rays. While the irradiated colonies remained free from gross and microscopic changes some of their descendants exhibited various and variable phenomena. These phenomena consisted primarily in pleomorphic degeneration and massive deterioration of the fuseaux formation. Presumptive evidence that these changes were the result of the irradiation is based on the following facts: (1) the degeneration phenomenon occurred in two experiments and the massive deterioration in four out of five experiments; (2) both reoccurred in successive generations of colonies, and (3) both were absent in the respective control colonies. Since occasional and rare distorted spindles could be detected in a few control colonies, and since pleomorphism is a "normal" event in the life history of M. canis, it is believed that the biologic downward trend of an aging strain was intensified and accelerated through the x-rays administered. Other changes, such as appearance of a M. gypseum-like variant or massive degeneration of the entire mycelium, were omitted from the list of presumable radiation effects. Their inclusion did not seem warranted because they were single occurrences.

VITAMIN A DEFICIENCY WITH CUTANEOUS, CONJUNCTIVAL ("BITOT" SPOTS) AND RENAL MANIFESTATIONS

Report of a Case

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IN RECENT years there has been interest in the lesions of the skin associated with vitamin A deficiency. Since Frazier and Hu first reported the syndrome in 1931[1] and subsequently investigated the cutaneous variations from infancy to puberty among Chinese children, there have been numerous studies from different countries, including our own.

The following case is being reported because, in addition to the interesting cutaneous lesions in a child, it presents accompanying ocular and renal manifestations of the vitamin A deficiency state. A search of the literature indicates that the circumscribed areas of xerosis of the conjunctiva ("Bitot" spots) and the metabolic calcinoses of both kidneys which were present in this child in combination with the skin lesions of avitaminosis A have not hitherto been described in the United States.

REPORT OF CASE

History.—F. L. D., a 10 year old white girl, was admitted to the John Sealy Hospital, Galveston, on March 4, 1947, with the complaints of anorexia, nausea and great weight loss. Her illness had begun 2½ years previously. In December 1944 the patient had had the "flu," with a high fever lasting two weeks. After this illness the patient increasingly lost her appetite, became weak, nervous, easily frightened and unable to go to school. Bowel movements became clay colored and frequent, and there had developed an almost constant "oily seepage" from the anus. Treatments, which had varied from oral tonics and vitamins, prescribed by several physicians, to whisky toddies twice daily, prescribed by a faith healer, had availed little. In recent weeks there had appeared small "pointed bumps" on the skin, which were attributed to the child's having walked through the woods and come into contact with "stickers." She was referred to the hospital by a physician who thought she might have tuberculosis.

Until the onset of the present illness the patient had enjoyed normal growth and health and had been mentally alert. The family history was noncontributory, both parents and six siblings enjoying good health.

Physical Examination.—The general appearance was that of a chronically ill, listless female child whose state of emaciation was striking. As she sat in a decidedly lordotic position, taking scant notice of her environment, the skin literally seemed to hang from her frame. Her cheeks were tinged pink, with the remainder of the skin very pale.

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1. Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated with Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507-514 (Sept.) 1931.

Skin and Dermal Appendages: The hair of the head was coarse and scanty, and the scalp was slightly scaly. The skin in general was xerotic, warm and rough. It had poor turgor. The skin over the abdomen, thorax, posterior and lateral surfaces of the arms, the elbows and the knees presented minute conical horny papules. These arose from the pilosebaceous follicles and were about 2 mm. in diameter. On palpation these hyperkeratotic lesions were found to give a "grater-like" feel to the skin. About the knees and elbows there were larger pinkish papules, evidently the site of perifollicular involvement, and inflammatory lesions due to secondary infection. There was no abnormal pigmentation of the skin. The large body folds were dry, as there was an apparent abeyance of sweating. The nails showed no significant abnormality. The mucous membranes of the mouth and nasopharynx appeared normal; the gums were slightly reddened, and there were many carious teeth. The tongue was bright red and showed some bald smooth areas and slight fissuring. The mucous membranes of the genitalia appeared moist and pale.

The Eyes: The conjunctivas of both eyes revealed the following four interesting lesions: On the bulbar conjunctivas there appeared well defined, slightly elevated pale yellowish white areas. They were triangular, measuring about 4 by 3 mm. (base and length). The bases were adjacent to the limbi, and the apexes pointed toward the canthi. The lesion on the temporal side of the limbus of the right eye was the most prominent. The palpebral and bulbar conjunctivas were pale; no petechiae or jaundice was noted; the media of the fundus was normal in each eye, and the extraocular movements and the pupillomotor mechanism were normal. Except for the presence of palpable cervical lymph nodes, the remainder of the physical and neurological examination revealed no abnormality.

Laboratory Data in Preliminary Work-Up.—Blood: The total red blood cell count was 3,020,000 per cubic millimeter, with 2.6 per cent reticulocytes, and 7.8 Gm. of hemoglobin (a normocytic hypochromic anemia). The total white blood cell count was 17,600, with the following differential: polymorphonuclear neutrophils, 79; stab forms, 1; polymorphonuclear eosinophils, 1; lymphocytes, 12, and monocytes, 7. The total platelet count was 980,000 per cubic millimeter.

Blood Chemistry: Total plasma proteins amounted to 6.29 Gm. (albumin, 3.2 Gm., and globulin, 3.09 Gm.), and fasting blood sugar, 48 mg. per 100 cc. The amounts of blood cholesterol, phosphorus, phosphatase, ascorbic acid, nonprotein nitrogen and serum calcium were all within normal limits.

Sternal Marrow Examination: Sternal marrow puncture revealed a slightly hypercellular marrow with a normal myeloid series. Megakaryocytes were abundant and qualitatively normal. There was, however, a pronounced erythroid stimulation at the normoblastic level.

Urine: The urine showed a specific gravity of 1.006, a few white blood cells and the presence of keratinized epithelial cells in a catheterized specimen. The latter were demonstrated with a Giemsa stain. Tests showed an inability of the kidneys to concentrate the urine to a specific gravity any higher than 1.006.

Stool Examination: On several examinations Giardia lamblia were demonstrated, as well as crystals of the fatty acid type, together with much vegetable and cellulose remains. There was no blood, pus, mucus or any other parasite present. A 5 per cent solution of stool gave a strongly positive reaction for undigested starch when treated with strong iodine (Lugol's) solution (the reaction of a control stool being negative). When this solution was stained for neutral fat globules with sudan III there was a highly positive reaction (60 per cent). Fat in feces amounted to 58.2 per cent of the dry weight (12 to 15 per cent, normal value). Special intestinal fat absorption studies initially revealed the virtual absence of fat absorption.

Other Studies: Fasting blood study revealed total fatty acids of 217 mg. per 100 cc., with an iodine number of 83.4. Four hours after 6 ounces (180 cc.) of 20 per cent butterfat cream had been taken, total fatty acids were 215 mg. per 100 cc., with an iodine number of 87.7.

Tuberculin (intradermal and patch), Schick, brucellergin, Kahn and Kolmer tests all elicited negative reactions. Gastric washings proved negative for acid-fast bacilli. An unsuccessful attempt was made to test trypsin activity.

X-Ray Studies.—Anteroposterior and lateral views of the abdomen showed collections of finely mottled opaque calcifications on each side of the abdomen overlying the kidney areas. The calcifications appeared to be intrarenal calcinoses of the renal pelves. With barium enema studies there appeared considerable redundancy in the colon throughout. The chest was normal roentgenologically.

Biopsy.—Histologic examination of a selected area showed a moderately thickened epidermis with a hyperkeratotic surface. There was a decided increase in the amount of fibrous tissue in the underlying corium with occasional sweat glands and hair follicles. The keratotic process extended well down into the follicles. The sweat glands showed no abnormality. Acid-fast stains gave negative reactions.

Corneal Microscopic Studies.—On microscopic examination it was revealed that the ocular lesions previously noted were thickened areas of bulbar conjunctiva which appeared highly refractile and of a pressed-out gelatinous or "frost glass" character. There were no blood vessels on or in these conjunctival lesions. The corneoscleral limbi revealed small (nonextensive) vascular arcades which took fluorescein stain.

Course in Hospital.—During the initial four weeks in the hospital, while undergoing preliminary laboratory procedures and tests, the patient was placed on a high caloric diet with frequent feedings plus the administration of iron and vitamin B supplements. There was a regular nocturnal fever, with temperatures ranging from 100 to 102 F. During this month the patient gained only 3 pounds (1.3 Kg.). The skin and conjunctival lesions remained the same. In the fifth hospital week the patient became afebrile and the blood picture changed to a macrocytic hypochromic type of anemia. Plans for biophotometric testing of dark adaptation, controlled determinations of the blood vitamin A levels and testing of the activity of the pancreatic enzymes unfortunately could not be carried out. With the advent of the Texas City disaster the patient was immediately evacuated from the hospital. Prior to her leaving she had been placed on treatment with the oral administration of 25,000 units of vitamin A in oil per day. It was intended that the patient receive much larger doses of this vitamin, but in the tumultuous conditions of the disaster days orders on nonemergency cases were not easily changed or followed.

Twenty-four days elapsed before the patient was again seen, on May 8, at a home for convalescents, some distance away. There had occurred a remarkable change. The child was alert, happy and active and had made a gain of 14 pounds (6.4 Kg.), which made her now appear chubby. The tongue was normal. The hair was growing back noticeably and was less dry than formerly. The body folds were moist. The follicular hyperkeratotic papules were less prominent on the legs and abdomen but appeared unchanged on the arms. The areas of localized conjunctival xeroses had totally disappeared. The sole "treatment" had been the normal house diet plus 25,000 units of vitamin A per day.

The fat absorption had meanwhile improved but was not yet normal. The results of a test done on May 14 were as follows: Fasting blood—total fatty acids, 200.7 mg. per 100 cc., with an iodine number of 108.5, and after the taking of butterfat—total fatty acids, 240.2 mg. per 100 cc., and an iodine number of 96.7.

Urine concentration tests were repeated and showed no significant change, the highest specific gravity obtained being 1.010. Repeat roentgenograms of the abdomen still showed the presence of opaque mottled calcifications in both kidney pelves. They appeared unchanged. Excretory urograms were not done because of the positive skin reaction to the test excretory dye. The stools were now negative for G. lamblia. The red blood cell count was now 3,900,000 with 10.1 Gm. of hemoglobin. The fasting blood sugar level was 95.7 mg. per 100 cc.

On June 21 a third intestinal fat absorption test showed that this function had practically returned to normal, as follows: Fasting blood—total fatty acids, 379.1 mg. per 100 cc., with an iodine number of 97.1, and four hours after butterfat meal—total fatty acids, 432 mg. per 100 cc., with an iodine number of 94.1.

Several days later the patient was lost from observation. When last seen she had practically doubled her admission weight and had no complaints. Follicular hyperkeratotic lesions were present in a diminished number on both arms, but the follicular and larger papular lesions on the trunk and lower extremities had disappeared without scarring. The conjunctival lesions had not reappeared. The hair, scalp and sweating functions had returned to normal.

COMMENT

Although one may speculate as to the fundamental nature of the illness which led to the vitamin A deficiency manifestation in this patient, the underlying etiology remains obscure. The acute febrile episode which the patient is said to have had when 7 years of age may have been the precipitating factor which led to her deficiency state. That cutaneous lesions of a vitamin A deficiency may follow a period of high fever has been noted before. As six siblings in the patient's family subsisted on the same diet and were well, it is not believed a deficient diet in itself played a factor. The diagnoses of celiac syndrome, indigenous sprue and lipophagia granulomatosis were considered. Although the relatively late onset in childhood, the blood picture and the rapid recovery in the course of the patient's observation make these questionable, they cannot be completely ruled out. It has been suggested that the intestinal parasite G. lamblia may, by coating the small intestine in a heavily infected child, act as a mechanical barrier to fat absorption and result in increased fecal fat excretion.[2] Although this patient was found to have giardiasis, the pathogenicity of the organism in her case cannot be evaluated, as the intestinal fat absorption improved without any specific parasiticidal therapy. From the laboratory data it is indicated that the fat, carbohydrate and, possibly, protein absorption were faulty. In this study we were primarily interested in the fat absorption in this patient. As crucial tests to study the pancreatic enzymes could not be done, in this respect one can only note that on admission the patient had abnormally poor fat absorption. The administration of fat-soluble vitamin A with the resultant improvement of lesions due to this deficiency may be accounted for by the return to normal function in the fat absorption mechanism. The tongue presented the sole grossly visible manifestation of a vitamin B deficiency. This cleared rapidly when treated. The small vascular arcades noted at the corneoscleral limbus probably represented changes due to a riboflavin deficiency.

The skin lesions in this patient were interesting in that, in addition to the generalized xerosis of the skin which is usually found in vitamin A-deficient children, there was also a diffuse eruption with intrafollicular hyperkeratoses easily visible to the naked eye. The papules which were present on this patient's extremities are rarely found in children. They are, however, frequently seen in the postpubertal age groups with this nutritional deficiency.[3] The rapidity with which the hyperkeratotic lesions on the lower extremities and trunk regressed with the use of relatively small doses (25,000 units daily) of vitamin A supplements is worthy of note.

The ocular manifestations of a vitamin A deficiency are xerosis conjunctiva and xerosis cornea leading to corneal turbidity, ulcer and keratomalacia. When the xerosis conjunctiva occurs in a small localized area which is typically triangular or wedge shaped, with the base adjacent to the limbus, and elevated above the rest of the conjunctiva so as to be well defined and of a white to yellowish color, it is generally called a "Bitot" spot.[4] Since Bitot's time there have been occasional

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4. Bitot, C.: Mémoire sur une lésion conjonctivale, non encore décrite, coincidant avec l'héméralopie, Gaz. hebd. de méd. et de chir. **10:**284-288 (May 1) 1863.

reports in the foreign literature of the occurrence of these ocular lesions in children. The subject of this study presented the typical Bitot spots, which disappeared completely within a 24 day period after oral vitamin A therapy was commenced in small doses. This patient did not have the corneal lesions found very late in the deficiency state and did not present the conjunctival pigmentation which has been observed in the Negro and yellow races.

Vitamin A deficiency causes specific pathological changes in many epithelial structures. This process has been termed metaplasia. After atrophy of the specific epithelium concerned,[5] there occurs reparative proliferation of the basal cells and differentiation of the new product into a stratified keratinizing epithelium. Regardless of the former anatomy and physiology of the organ, the replacement epithelium is identical wherever located and in all its layers becomes comparable with epidermis.[6] A lack of vitamin A is a cause of renal stone in the experimental animal. Experimentally the desquamation of the keratinized epithelial cells of the renal pelvis caused by avitaminosis A may form the nidus for a calculus.[7] The striking geographical distribution of urinary stones, especially in children, suggests a relationship with that of vitamin A deficiency syndrome. In Egypt, India and Far Eastern countries urolithiasis is commonest in children (in Europe and America children are rarely affected with urinary stones, while the older age groups are). Also, it is interesting to note that a century ago the formation of renal stones was quite frequent among European children. There is certainly a suggestion that the improved diet over the years may well explain the change.

The presence of the keratinized epithelial cells in the urine of this patient, the finding of bilateral intrarenal calcinoses and the poor results of the urine concentration tests strongly indicate that a metaplasia of the renal epithelial cells in the kidney pelves and upper ureters may have altered the renal physiology so as to account for the defective reabsorption by the tubules, with resulting impaired concentrating power.

SUMMARY

A case of vitamin A deficiency is reported with general xerosis and follicular hyperkeratotic and papular skin lesions. The classic conjunctival "Bitot" spots (localized xerophthalmia) were present, and probable metabolic calcinoses of both kidneys were demonstrated. Keratinized epithelial cells were found in catheterized urine specimens with a Giemsa stain. Urine concentration tests showed poor concentration. Results of special fat absorption studies, which initially revealed the virtual absence of fat absorption, returned to normal as clinical improvement occurred. With the administration of small doses of vitamin A the cutaneous and ocular lesions improved. The renal lesions appeared unchanged. A search of the available dermatologic and pediatric literature does not reveal a previous description in this country of a similar pediatric case with cutaneous, ocular and renal manifestations of the vitamin A deficiency syndrome.

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NECROBIOSIS LIPOIDICA DIABETICORUM: ITS SURGICAL TREATMENT

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NECROBIOSIS lipoidica diabeticorum is practically always a therapeutic enigma. This paper describes a surgical method of treatment, the results of which suggest that it may be employed to advantage in severe and disabling cases of the disease.

Originally believed to be a rare disorder, necrobiosis lipoidica diabeticorum has been recognized with increasing frequency during recent years. Diabetes mellitus is found to be coexistent with it in 80 to 90 per cent of cases, but a sequential relationship has not been definitely established. More than 80 per cent of patients who have the disease are women.[1] The lesions almost always occur on the shins, although they have also been encountered on the thighs, arms, abdomen, breasts and other parts of the cutaneous surface. Trauma appears to be an instigating factor in some cases of the disease, and the lesions frequently progress to the stage of ulceration after trauma.[1] Both legs are involved in more than half the cases.[1] Ulceration occurs in 25 to 50 per cent of cases,[1] and the condition then requires careful study to distinguish it from the multitude of diseases which are associated with ulcers of the legs. The patient with extensive and ulcerated necrobiosis lipoidica diabeticorum is wretched and frequently incapacitated.

The clinical features enable the diagnosis of necrobiosis lipoidica diabeticorum to be established in most instances. Pathologic examination is of distinct help in doubtful cases. Microscopic study shows poorly defined areas of necrobiosis involving the collagen of the dermis accompanied with an inflammatory infiltrate which contains lymphocytes, histiocytes, fibroblasts and foreign body giant cells. In addition, there is extracellular deposit of various lipids which can be demonstrated with fat stains. Vascular alterations are conspicuous and significant. The vessels of the middle and lower parts of the dermis show endothelial proliferation and fibrosis of their walls, and the process sometimes results in complete occlusion of the lumen.[2] These vascular changes, which account for the degeneration of the dermal collagen [2] and in large measure for the ulcerations, have deterred previous attempts at excision and replacement of diseased tissue with grafts.

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The treatment of necrobiosis lipoidica diabeticorum is singularly ineffectual. Control of the diabetes, injection of insulin directly into the lesions, a low fat diet, the administration of tocopherols and actinic therapy have all been employed without success.

REPORT OF A CASE

Mrs. J. W., a 57 year old white woman, the wife of a farmer, came to the hospital for the first time in December 1947. She related that she had had lesions on the anterior surface of each leg for approximately five years. These had slowly increased in number and size. In 1944 the lesions became ulcerated, and by 1946 the patient was able to be up and about for only an hour or so each day. Her past history was not otherwise remarkable.

Fig. 1.—*A*, ulcerated necrobiosis lipoidica diabeticorum involving the right leg of the patient described in this communication. The left leg, which had looked exactly like the right, had already been operated on when this photograph was made. *B*, a photograph was made three weeks after the operation on the right leg and six months after the operation on the left leg. The two small denuded areas on the anterior aspect of the right leg were healed within a few days after this picture was taken, and there was no evidence of recurrence of the disease in the grafted sites at the time of writing.

Examination showed an obese white woman who had many discrete and confluent dime-sized to half-dollar-sized ulcers on the anterior middle third of each leg (fig. 1 *A*). The skin surrounding the ulcerated areas was atrophic and had a glazed, yellowish appearance. Peripherally the entire lesion was encompassed by a purplish zone of infiltration. Physical examination revealed an otherwise normal condition. The clinical diagnosis was necrobiosis lipoidica diabeticorum with extensive and severe ulceration.

Laboratory studies were productive of the following results: Examination of the blood showed the red blood cell count to be 4,380,000 and the white blood cell count 6,500 with a normal differential count. Hemoglobin was 110 per cent. Urine examination gave normal results. A glucose tolerance test indicated that the patient had mild diabetes mellitus. A biopsy

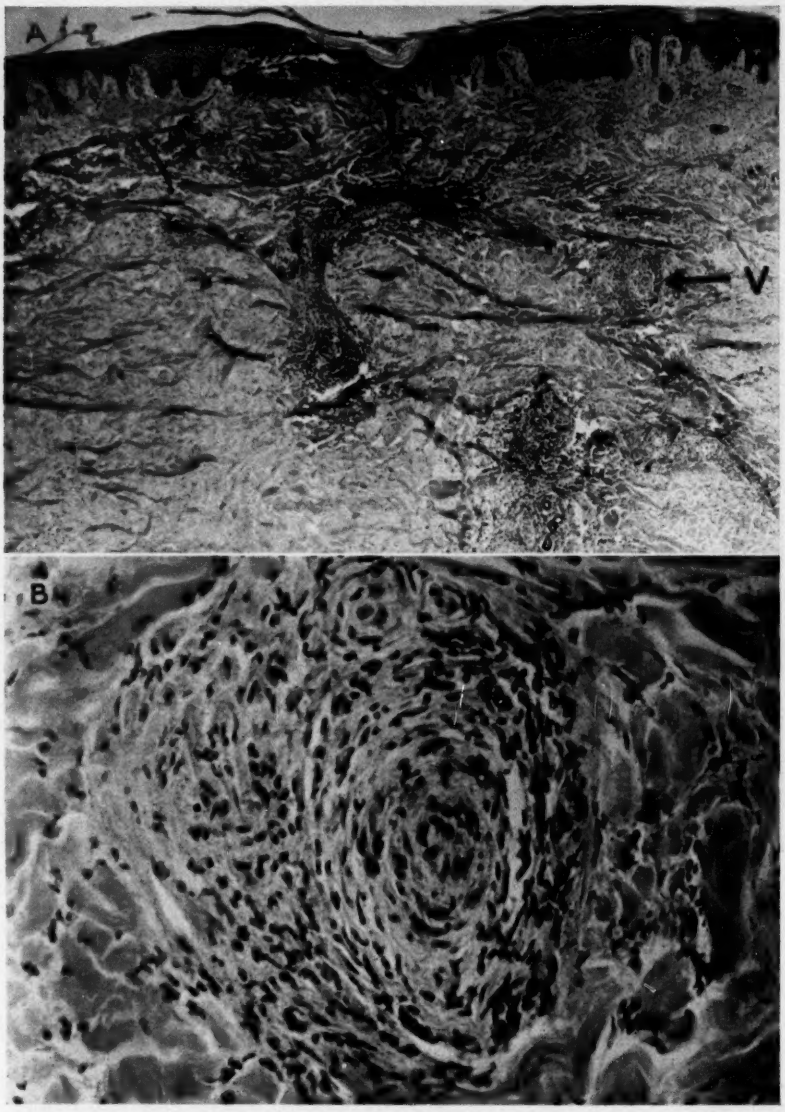

Fig. 2.—*A*, biopsy specimen from a nonulcerated portion of the lesion shown on the right leg in 1 *A*. The large, poorly defined and pale-staining zones represent areas of necrobiosis, throughout which the collagen is homogenous and swollen. The inflammatory infiltrate is present at the periphery of these zones and about appendages and blood vessels. The vessel at *V* is completely occluded, as shown in *B*. *B*, high power view of the blood vessel shown at *V* in *A*. Its lumen is completely occluded by endothelial proliferation and fibrosis of its wall.

specimen removed from one of the yellowish plaques showed microscopic features which bore out the clinical diagnosis of necrobiosis lipoidica diabeticorum (fig. 2). The blood Kahn reaction was negative, and all other laboratory studies yielded results that were normal.

The patient was treated conservatively for two months at bed rest. Silver nitrate wet dressings were applied to the ulcerated areas alternately with penicillin ointment. Also, penicillin was given intramuscularly. Because of her obesity the patient was placed on a reduction diet. Her diabetes mellitus was so mild that it did not require treatment. The secondary infection of the legs cleared promptly, but the ulcers were refractory.

Available evidence and previous experience with similar cases indicated that the ulcers would probably persist indefinitely and the patient continue to be incapacitated. When the entire situation was explained to her, she chose to have one leg operated on, with the realization that the underlying occlusive vascular disease might completely negate the results. On March 1, 1948 an Esmarch bandage was placed on the left leg in order to expel the blood from the extremity. A tourniquet was then applied for the duration of the operation and the Esmarch bandage removed. This procedure resulted in an almost bloodless operative field. The involved area was outlined by sharp incision and the encompassed tissue dissected downward to deep, underlying fascia. Two complete dermatome drums of skin from the thigh, each measuring 4 by 8 inches (10 by 20 cm.) and 20/1,000 inch (0.5 mm.) thick, were required to cover the defect. The grafts were sutured in place with 0000 dermalon® and covered by a light fluff dressing. Some pressure was applied by the use of Ace type elastic bandages, and the tourniquet was removed after all dressings were in place. A similar operation was performed on the right leg on Aug. 9, 1948. In both instances there was complete "take" of the grafts, and by September 10 the patient was ambulatory (fig. 1*B*). She was seen on several subsequent occasions and was able to live as she did before the onset of the disease, working 12 to 14 hours each day. Two years after the last operation, she was completely well. There was no evidence of a recurrence of the disease in the grafted sites.

COMMENT

The hazard of attempting to evaluate a therapeutic procedure on the basis of its trial in one case is apparent. The excellent results achieved in this instance, however, should encourage intervention by others who may be deterred from attempting surgical treatment of necrobiosis lipoidica diabeticorum because of the underlying occlusive vascular changes.

Clinical Notes

USE OF N-ETHYL-O-CROTONOTOLUIDIDE FOR THE RELIEF OF PRURITUS

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AND
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In 1946 Domenjoz[1] reported on the development and clinical use of N-ethyl-*o*-crotonotoluidide,[2] a newly synthesized scabicide. Additional reports[3] emphasizing its scabieticidal properties and lack of local or systemic reactions soon appeared. In 1949 its use both as a scabicide and as an antipruritic agent was reported by Couperus,[4] who obtained in 70 cases of scabies 100 per cent cure and in 124 cases of a variety of dermatoses complete relief from pruritus, lasting six to eight hours, in 66.2 per cent, moderate relief in 27.4 per cent and little or no relief in 6.4 per cent. Impressed with the antipruritic virtues of N-ethyl-*o*-crotonotoluidide cited by Couperus, we treated 121 patients representing all age groups and both sexes, some of them for

Effect of N-Ethyl-o-Crotonotoluidide on Pruritus

Diagnosis	Total No. of Cases	Results			Local Reactions
		Excellent (Complete Relief)	Moderate (Considerable Relief)	Fair (Slight or No Relief)	
Neurodermatitis (including atopic dermatitis)	34	17	13	3	1
Lichen planus	4	1	3	..	..
Dermatitis venenata (subacute)	15	2	5	7	1
Hodgkin's disease	2	..	2	..	..
Psoriasis (generalized)	1	1	..	..	..
Seborrheic dermatitis	2	..	2	..	..
Dermatitis hiemalis	1	..	1	..	..
Infectious eczematoid dermatitis	7	3	2	1	1
Diabetic pruritus	2	..	2	..	..
Impetigo (bockhardt)	1	1	..	..	..
Lichen simplex	17	2	10	4	1
Pemphigus vulgaris	2	..	2	..	..
Pustular bacterid	2	2	..	..	..
Pruritus of unknown etiology	17	5	10	2	..
Dermatitis herpetiformis	4	..	..	3	1
Pruritus ani, vulvae or scroti	10	2	3	5	..
Totals	121 (100%)	36 (29%)	55 (45.3%)	25 (20.7%)	5 (4%)

over a year, to see whether the drug's antipruritic properties persisted with continued use and whether long usage caused local reactions. In all cases in which excellent relief with 10 per cent

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1. Domenjoz, R.: A New Scabicide, Schweiz. med. Wchnschr. **76**:1210-1213 (Nov. 23) 1946.

2. This preparation was supplied by the Geigy Company, Inc., New York, in a 10 per cent concentration in a vanishing cream base and is marketed under the name eurax.®

3. (*a*) Burckhardt, W., and Rymarowicz, R.: Experience with the New Scabicide, Eurax (Geigy), Schweiz. med. Wchnschr. **76**:1213-1214 (Nov. 23) 1946. (*b*) Lenggenhager, R.: Experience with New Scabicides, Praxis **36**:465-466 (June 26) 1947. (*c*) Boer, R.: Antiscabietics, Nederl. tijdschr. v. geneesk. **92**:3119-3120 (Oct. 2) 1948. (*d*) Dorner, G.: The New Antiscabies Preparation, Eurax, Deutsche med. Rdschau. **3**:422, 1949. (*e*) Tronstein, A. J.: Ten Per Cent Crotonyl-N-Ethyl-O-Toluidine Ointment (Eurax), A New Scabieticidal Agent, Ohio M. J. **45**:839-891 (Sept.) 1949.

4. Couperus, M.: The Use of N-Ethyl-O-Crotono-Toluidide in the Treatment of Scabies and Various Pruritic Dermatoses, J. Invest. Dermat. **13**:35-42 (July) 1949.

N-ethyl-*o*-crotonotoluidide in a washable ointment base was shown no relief was obtained with a placebo. A majority of the patients with neurodermatitis or other long-standing pruritic dermatoses, who had applied a variety of medications, repeatedly requested additional ointment, stating that, although it did not cure the ailment, it controlled pruritus better than did any other preparation; also, it was desirable because of its lack of odor, lack of staining and nonaggravation of any coexisting pyodermas.

In addition to producing good results in the various conditions mentioned in the chart the preparation has been found by Couperus [4] to be effective for pruritus accompanying varicella, dermatophytosis, lupus erythematosus, urticaria, neurotic excoriations, stasis dermatitis, creeping eruption, erythema solare, pompholyx, fixed drug eruption, pityriasis rosea, insect bites and catarrhal jaundice, and Tronstein [3e] observed a favorable action of the drug on "diaper rash."

SUMMARY

One hundred and twenty-one patients with pruritic dermatoses were treated with 10 per cent N-ethyl-*o*-crotonotoluidide in a vanishing cream base. Excellent to moderate relief was observed in 74.3 per cent of this group and local reactions in 4 per cent. Use of the drug for over a year did not decrease its usefulness as an antipruritic agent or cause local reaction.

TRICHONODOSIS

Report of a Case

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Trichonodosis (knotted hairs) may affect any of the various types of hairs located on the body. Two types of trichonodosis are generally described: (1) a rare variety of undetermined etiology associated with abnormal hair growth and (2) a commoner variety resulting from physical and mechanical forces. The etiology, I believe, is purely mechanical whether the knotted hairs occur in normal or abnormal hair growth. The pubic and thigh regions are most frequently involved since curliness of the hairs in those areas predisposes them to knotting. Mechanical factors such as scratching, combing, washing or friction may produce tangling and knotting of hairs. Repeated encounter with these factors results in tightening of the knots. If the knots are pulled excessively tight, transverse splintering of the hair shaft and simulation of trichorrhexis nodosa may result. Cases resembling alopecia, due to the breaking off of the hairs at the knots, have been reported.

Usually not all the hairs are involved. Single-knotted hairs are most characteristic, although some hairs may have several knots. These knots simulate so closely the ova deposited by body, head and pubic lice that microscopic examination is often necessary for differentiation.

McCarthy [1] in 1940 stated he could find no report of trichonodosis in the American literature. Since then A. G. Pratt [2] and M. A. Weiner [3] have each reported a case. All agree the condition is not rare. Since the condition is of little more than academic interest some may wonder why any cases have been recorded. Undaunted, however, I believe the following case to be of interest in view of the fact that pediculosis and trichonodosis were present simultaneously.

REPORT OF CASE

In October 1949 a 30 year old white soldier was seen in the Dermatology Clinic at the Ninety-Eighth United States Army General Hospital in Munich, Germany, for a noncontributory

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* Formerly Captain, Medical Corps, Chief of Section on Dermatology and Syphilology, Ninety-Eighth United States Army General Hospital, European Command.

1. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, pp. 103-104.

2. Pratt, A. G.: Trichonodosis: Report of a Case, Arch. Dermat. & Syph. **56**:267-269 (Aug.) 1947.

3. Weiner, M. A.: Trichonodosis: Report of a Case, Arch. Dermat. & Syph. **58**:238-240 (Aug.) 1948.

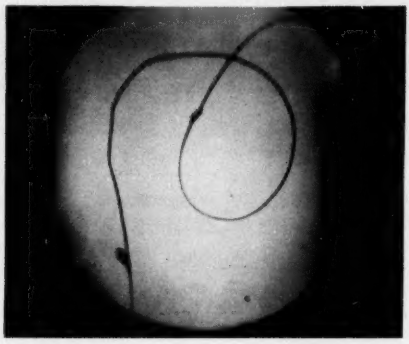

Fig. 1.—Photomicrograph of a pubic hair demonstrating the presence of a nit (lower left corner) on the proximal aspect of the hair shaft. A knot is present near the center of the photograph on the distal portion of the hair shaft.

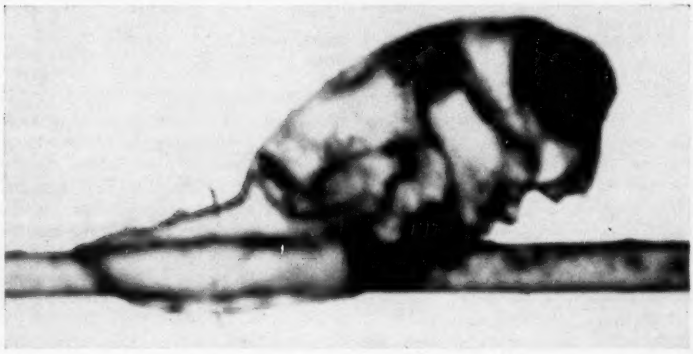

Fig. 2.—Photomicrograph of the nit.

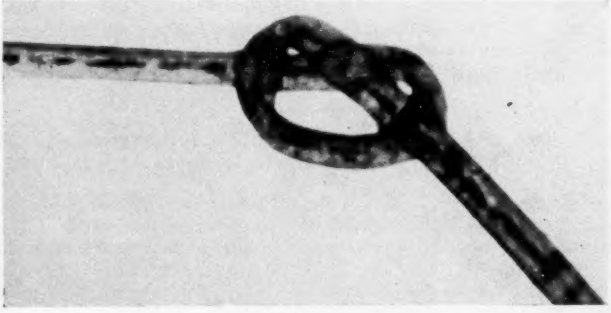

Fig. 3.—Photomicrograph of the knot.

dermatitis. During the routine physical examination small, barely visible nodular masses were noted on the distal half of numerous hair shafts in the thigh and genital regions. Grossly similar but slightly larger masses were located on the proximal portion of approximately five hair shafts in the pubic area. The axillary and scalp hairs were normal. Careful observation did not reveal lice in any region of the body or on the man's clothing. Pubic pruritus was denied. The patient had no prior knowledge of the existence of these nodules, nor did he appear unduly impressed after having them shown to him. Microscopic examination revealed the more numerous distal nodules to be tightly knotted portions of hair and the proximal nodules to be ova of pediculi. Since no lice were discovered, the exact variety of pediculi could not be determined. It is fairly reasonable to assume, however, that the ova were deposited by Phthirus pubis.

In trichonodosis the knots are generally located on the distal half of the hair shaft. In pediculosis pubis the nits are invariably located on the proximal portion of the hair shaft. The location of the nodules may therefore often be of diagnostic value in the differential diagnosis.

NEW ULTRAVIOLET GENERATOR FOR USE IN THE DIAGNOSIS OF TINEA CAPITIS BY FLUORESCENCE

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LOS ANGELES

I have tested a new source of ultraviolet radiation [1] and have found it to furnish adequate intensity for the diagnosis of tinea capitis by fluorescence. In addition, it possesses several advantages not heretofore available. It is light, compact, durable and easily transported in the pocket. It consists of a single unit, roughly cylindrical, approximately 2 inches (5 cm.) in diameter and 10 inches (25 cm.) in length, containing the transformer in the handle and weighing only 19 ounces (570 Gm.), including the electrical cord and plug. Its radiation is concentrated almost entirely at 3,660 angstrom units, thereby eliminating the dangers of radiation in the therapeutic range. The lamp requires only a momentary "warming-up" period before reaching its maximum intensity, remains cool in use, does not go out if jarred or jolted and can be immediately relighted without an interval for cooling. The burner is reputed to have an exceptionally long life. The apparatus is not expensive. The following discussion may serve to illustrate my reasons for recommending it for dermatological use.[2]

Ultraviolet radiation in a dark room causes some objects to fluoresce with a characteristic hue. This phenomenon is useful in diagnosis of a few diseases, the best example of which is tinea capitis. In some forms of this disease the hairs infected with the fungus assume a brilliant greenish yellow color while the normal hairs do not.

This phenomenon occurs with ultraviolet radiation of a wide variety of wavelengths covering at least the range from 2,537 to 3,660 angstrom units; each of these figures represents a band capable of exciting an intense fluorescent response. Radiation at 2,537 angstrom units, however, is also effective therapeutically and must be handled with all the precautions with which such therapy is surrounded; that at 3,660 angstrom units is free from this effect. It seems wise, therefore, to employ the longer, safer wavelength for diagnostic purposes.

The two types of generators of ultraviolet radiation which are in general use, known as the cold quartz and mercury vapor lamps, produce entirely different spectrums, that from the former almost entirely (90 per cent) at 2,537 angstrom units, and that from the latter scattered above that point over the entire range upward into the visible spectrum, exhibiting a strong band in the region of 3,660 angstrom units. With appropriate glass filters it is possible to remove from either spectrum all but the 3,660 band, after which radiation from mercury vapor lamps is still intense enough for diagnostic purposes; that from cold quartz generators is not, consisting of but 2 or 3 per cent of the radiation originally developed.

From the Department of Dermatology and Syphilology, University of Southern California School of Medicine.

1. Mineralight SL 3660,® Ultra Violet Products, Inc., 145 Pasadena Avenue, South Pasadena, Calif.

2. My attention was directed to this instrument by Dr. Henry G. Morgan of Los Angeles.

The mercury vapor lamp has several objectionable features from which the cold quartz type is free; it is more expensive to produce and maintain, has a much shorter life span and becomes very hot while in use. In fact, it must reach a relatively high temperature before becoming efficient and hence cannot be used for the first few minutes after being lighted, and if turned off cannot be relighted until cool. Too much heat is generated to allow the lamp to be brought close to the patient's skin, an important factor because of the inverse square relationship of intensity of radiation, which, of course, influences the brightness of the fluorescent response. It has always seemed desirable to combine the good features of each burner if that were possible.

Such a combination appeared feasible when it was recalled that all commercial "fluorescent" lighting depends on the production of ultraviolet radiation within a vacuum tube by the cheaper cold quartz method (2,537 angstrom units); the wavelength produced is then transformed into visible light of whatever color is desired by a coating on the inside of the tube containing an appropriate substance termed a "secondary phosphor." Similar substances are also known which are capable of changing the 2,537 angstrom unit wavelength to 3,660 angstrom units, and one lamp has been available for several years which utilized this principle.[3] Its wattage was low, however, and in practice the radiation proved to lack the desired intensity, partly because of the elongated tubular form of the apparatus, which failed to concentrate the radiation at any particular point. Inquiry produced the information from the manufacturers that the development of generators of this type with increased potency must await a commercial demand greater than that anticipated for medical diagnostic use alone.

The largest commercial outlet for generators of fluorescent radiation has been sale to mineralogists, both professionals and amateur hobbyists. Until recently the instruments employed by them have all utilized the cheaper cold quartz principle. The recent discovery that certain minerals (notably some containing uranium), some oil cores and vitamin A exhibited fluorescence at 3,660 better than at 2,537 angstrom units has at last made the manufacture of the ideal generator for our purposes commercially feasible.[1] This manufacturer at least is now furnishing "mineralights" in two types, one of which emits radiation at 2,537 angstrom units, and the other, at 3660 angstrom units. The latter is an ideal source of "dark light" for dermatological use.

SUMMARY

A new source of ultraviolet radiation has been tested and found to offer several advantages over all generators heretofore available for detection of the fluorescence phenomenon in the diagnosis of tinea capitis.

3. No. 360 BL lamp, Sylvania Electric Company, Salem, Mass., and General Electric Company, Lamp Department, Nela Park, Cleveland.

GENERALIZED HERPES ZOSTER: REPORT OF A CASE FOLLOWING ROENTGEN RAY THERAPY, ASSOCIATED WITH CHRONIC LYMPHATIC LEUKEMIA, LEUKEMIA CUTIS AND MIKULICZ'S SYNDROME

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The association of herpes zoster with other diseases has always presented a fascinating study. As late as 1937 one author[1] divided herpes zoster into two distinct groups: (1) idiopathic, or primary, zoster, due to a virus, and (2) symptomatic, or secondary, zoster, caused by various chronic infections, by toxic drugs and by blood diseases. We now think that in all types the disease is probably caused by a virus, the activation of which may be caused by a variety of stimuli. The relationship of this virus to varicella is still not clear, and the generalized form of the disease was early thought to be due to the fortuitous occurrence of zoster and chickenpox. It is now thought, however, that the generalized eruption represents an extension of the zoster itself. Just what the factors are which cause the disease to become generalized is not known.

1. Ferreira, M. J.: Herpes Zoster Generalisatus in Leukemia, Arch. f. Dermat. u. Syph. **176**:295, 1937.

The association of generalized herpes zoster with lymphatic leukemia is well established, and a large number of such cases have been reported. Ferreira [1] in 1937 reported 42 cases in which herpes zoster appeared concurrently with leukemia of various types. In 34 it was with lymphatic leukemia; in three, with aleukemic lymphatic leukemia; in three, with myeloid leukemia, and in two, with a type of leukemia which was not indicated. Twenty-three of these cases presented generalized zoster. In the other 19 cases sufficient data were not given on the distribution of the lesions to permit a classification on this basis. Eleven of the patients had had roentgen therapy, but seven of these had also had treatment with arsenicals.

A review of the literature by Wile and Holman [2] in 1940 disclosed 32 cases of generalized herpes zoster in association with leukemia. The leukemia in 27 of the 29 cases in which the type was given was lymphatic. Wile and Holman commented on the high incidence of the disease in males (71.4 per cent). They also added two cases of their own, in both of which the patients had lymphatic leukemia, with roentgen ray therapy preceding the onset of the zoster. Several authors [3] have reported isolated and small groups of cases in which generalized herpes zoster was not associated with any other disease entity. All authors comment on the pleomorphism of the skin picture and the severe gangrenous nature of the primary zoster lesions.

A recent paper [4] reported a case associated with lymphatic leukemia in which biopsy of both primary and secondary zoster lesions revealed an actual leukemic infiltrate in the skin. The authors considered the occurrence of this phenomenon to represent merely a traumatic damage with subsequent leukemic infiltrate at the damaged site. Their case was the seventh such case proved by biopsy reported in the literature.

Because of the rarity of the generalized type of zoster and because in this case a combination of some very unusual features other than zoster were observed, the following case is presented.

REPORT OF A CASE

A 47 year old Negro was admitted to the hospital on Dec. 16, 1949, with complaints of enlarged lymph nodes, fever and a generalized blister-like skin eruption. He had been in good health until about one year before, at which time he had begun to note painless enlargement of the lymph glands in his neck. These grew quite rapidly and then became stationary. About six months before admission he noted enlarged lymph nodes in both groins and was given "several x-ray treatments" to these with no benefit. A little later he began to note a feeling of heaviness and severe pressure in the left upper portion of the abdomen. Five weeks before admission he noted several small, painless lumps in his scalp which grew quite rapidly, and about the same time he noted a swollen, red, tender lump at the inner canthus of his left eye and enlargement of all his salivary glands.

About two weeks before admission to the hospital, he was seen as an outpatient in the tumor clinic, where a diagnosis of lymphatic leukemia was made; roentgen ray therapy was administered to his neck, spleen, groins, axillas, eye and scalp tumors.

About one week after this treatment he noted the onset of a severe, burning pain commencing in the lower part of the thoracic region and radiating around the lower left portion of the chest wall to the midline anteriorly. Three days later he broke out with innumerable blisters on the lower left part of the chest and upper abdominal wall. Two days after this eruption he noted the appearance all over his body of pruritic but painless chickenpox-like lesions, and several of these lesions were noted inside his nose and mouth.

He had never had chickenpox and did not know of any recent exposure. No one in the family had had any recent fever blisters or any other herpetic disease. His health previous to

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2. Wile, U. J., and Holman, H. H.: Generalized Herpes Zoster Associated with Leukemia, Arch. Dermat. & Syph. **42**:587 (Oct.) 1940.

3. Steur, F.: A Rare Case of Generalized Gangrenous Herpes Zoster, Wien. med. Wchnschr. **61**:1167, 1911. von Zumbusch, L.: Generalized Herpes Zoster with Transformations of the Spinal Cord, Arch. f. Dermat. u. Syph. **118**:823, 1914. Pallasse and Delorme: Cervical Zona with Generalized Eruption, Lyon med. **128**:393, 1919. Barker, L. P.: Generalized Herpes Zoster: Report of 9 cases, Arch. Dermat. & Syph. **40**:974 (Dec.) 1939.

4. Barton, R. L., and O'Leary, P. A.: Herpes Zoster Generalisatus Associated with Chronic Lymphatic Leukemia, Arch. Dermat. & Syph. **51**:263 (April) 1945.

one year before had been excellent, but during the past six months he had lost about 15 pounds (7 Kg.). He had taken no drugs.

Physical Examination.—The temperature was 101.6 F.; the pulse rate, 104; respirations, 24, and blood pressure 128/80. The patient was a large, well developed and fairly well nourished middle-aged Negro who appeared acutely ill. There was some pallor of the mucous membranes. There was a large bandlike area of closely packed vesicles occupying the region of the tenth,

Severe gangrenous zoster lesion with generalized vesicles. Note the axillary mass.

eleventh and twelfth thoracic segments and the first and second lumbar segments on the left. This measured about 20 cm. in its greatest width. The skin was black in this area; many of the individual lesions had sloughed, leaving ulcers with red, clearcut margins. Scattered over the entire remainder of the skin were about 200 small, pea-sized, flaccid vesicles containing cloudy or hemorrhagic fluid. Some of these vesicles were set on normal or slightly erythematous skin, while others surmounted definite indurated nodules measuring up to 1.5 cm. in diameter. Many of the secondary vesicles were excoriated, leaving denuded red areas about 0.5 cm. in

diameter. There were several shallow ulcers on the buccal mucous membrane, and the left nostril was occluded with a large crust. The head showed three wartlike cauliflower tumors in the scalp; the largest measured about 3 cm. in diameter and 0.7 cm. in thickness. The surfaces of these masses had a glazed, pink, lobulated appearance. There was enlargement, redness and induration of the left lacrimal gland, with a small draining sinus in the overlying skin. The left submaxillary gland and both parotid glands were enlarged, firm and nontender. The neck was not stiff. There was enlargement of the lymph nodes in both anterior and posterior cervical chains and in both supraclavicular regions. These nodes measured up to 3 cm. each in diameter, were freely movable, soft and nontender, with no attachment to the overlying skin. There were large masses measuring 10 cm. each in diameter occupying both axillas. Examination of the heart and lungs revealed no abnormality. There was no increase in the retromanubrial dulness. The spleen extended to the umbilicus and was hard, smooth and slightly tender. The liver was palpable 4 cm. below the right costal margin. No other abdominal masses were noted. There were large ropelike masses of lymph nodes in both inguinal regions measuring about 12 cm. in length and 3 cm. in diameter. The extremities showed enlarged epitrochlear nodes on both sides but were otherwise normal except for the involvement of the skin.

A roentgenogram of the chest showed clear lung fields with no demonstrable mediastinal involvement. The red blood cell count on admission was 3,090,000; hemoglobin, 58 per cent, and white blood cell count, 130,000, with 99 per cent small lymphocytes. The blood smear showed an occasional nucleated red cell, but no immature white cells were noted. The results of urinalysis were within normal limits, and the Kahn reaction was negative. A biopsy of the largest scalp tumor showed slight flattening of the epidermis and infiltration of the corium with masses of small mature lymphocytes. There was no pleomorphism, and no mycosis cells were noted. No giant cells were seen. Biopsy was not done of the zoster lesions.

The patient was given chloramphenicol (chloromycetin®) and priscoline® (2-benzyl-4,5-imidazoline hydrochloride) and received two 500 cc. transfusions of whole blood. The gangrenous zoster areas were treated at first with boric acid compresses and later with calamine lotion. After about 10 days they scabbed over, at which time the entire area was dressed with sterile petrolatum. The secondary zoster lesions required no treatment other than application of calamine lotion and formed small, clean crusts which came off after about a week, leaving normal skin with residual pigmentation. The patient was discharged from the hospital on Dec. 29, 1949, with a red blood cell count of 3,520,000 and hemoglobin of 79.9 per cent; the white blood cell count had increased to 230,000, with 85 per cent small lymphocytes and 15 per cent immature granulocytes.

After discharge, he was followed as an outpatient, receiving additional transfusions and roentgen ray therapy. The zoster area which was gangrenous completely healed, with considerable scarring and pigmentation of the skin. The leukemia cutis lesions were easily controlled with roentgen ray therapy, and there was satisfactory healing of the lacrimal gland and shrinkage of the salivary glands. A small area of what was thought to be leukemic infiltration of the skin developed just under the left nostril. This also responded to roentgen ray therapy. Numerous blood counts were done, revealing hemoglobin values ranging from 60 to 80 per cent and white blood cell counts fluctuating between 20,000 and 100,000, with at least 95 per cent small mature lymphocytes. No other zoster lesions developed. The patient was last seen by me in June 1950.

COMMENT

There have been two established types of generalized zoster noted. In the first there is a successive involvement of different levels corresponding to the zonal distribution of a cranial or segmental nerve, accompanied with pain and other symptoms of the initial zoster lesion, no matter how many different areas are involved. The second, more frequent type is that in which the local zoster is followed by a scattered chickenpox-like eruption which is painless and which heals without scarring. A third type, the so-called "vesicules aberrantes," in which a small number of scattered vesicles appear at various sites removed from the initial lesion, has also been described. This is said to be relatively common.

The case presented corresponds clinically to the description of the second type and constitutes an instance of the well known association of this type with lymphatic leukemia, lymphomas and other lymphoid diseases. This case also presents very unusual-appearing gross lesions of

leukemia cutis, as well as an incomplete Mikulicz syndrome. I have been unable to find a report of a case in the literature exactly like this one. The associated proved leukemic infiltrations of the skin, however, make it very likely that the zoster lesions would also have shown lymphocytic infiltrate in connection with the vesicles. Unfortunately a biopsy was not done on the zoster lesion.

Whether herpes zoster in leukemia is due to a primary infiltration of the central nervous system or peripheral ganglions with leukemic cells or whether these cells are secondary to the damage caused by the specific virus remains an unsettled question. Complete autopsy studies on patients such as this need to be done and might shed further light on these questions.

SUMMARY

A case of generalized herpes zoster associated with lymphatic leukemia, an unusual form of leukemia cutis and Mikulicz's syndrome is presented.

The Harbin Clinic.

FIXED DRUG ERUPTIONS DUE TO SULFONAMIDES

A Report of Three Cases

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Fixed drug eruptions caused by sulfonamides have rarely been observed. Since Loveman and Simon [1] reported the first case of this phenomenon in 1939, only 12 additional cases have been recorded.[2] When one considers the incalculable quantity of sulfonamides that has been consumed and recalls the frequency of other cutaneous reactions to these drugs, it becomes apparent that fixed eruptions instigated by the sulfonamides are exceedingly rare. The cases described below have in no way differed in their clinical morphological aspects from the type of case originally described by Brocq.[3] Three examples of fixed drug eruption caused by sulfonamides were recently observed in the University Hospital Clinic within a period of one month.

REPORT OF CASES

CASE 1.—R. T. S. (#678947), a 26 year old premedical student, had had a persistent patch of hyperpigmentation on the left anterior aspect of the chest for 1½ years. On three occasions this lesion had become elevated, reddened and pruritic, but the flare-up had subsided within

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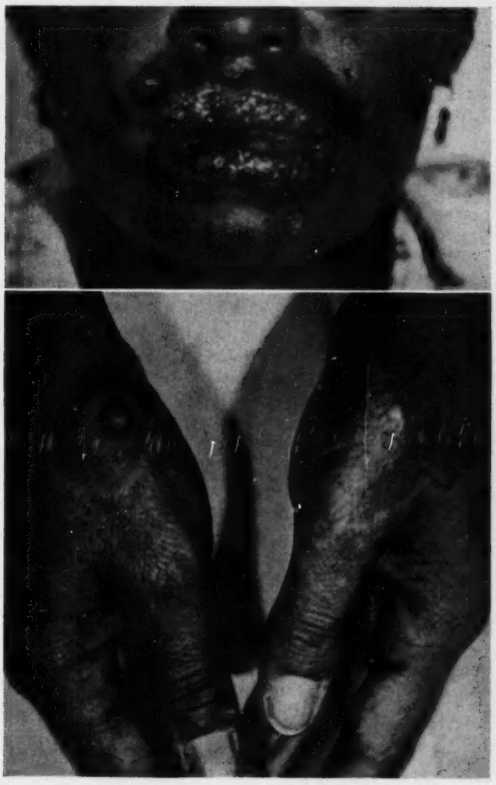
1. Loveman, A. B., and Simon, F. A.: Fixed Eruption and Stomatitis Due to Sulfanilamide, Arch. Dermat. & Syph. **40**:29 (July) 1939.

2. Goodman, M. H., and Arthur, R. D.: Fixed Eruptions: Report of Unusual Condition Due to Sulfanilamide, Arch. Dermat. & Syph. **43**:692 (April) 1941. Leifer, W.: Fixed Sulfathiazole Eruption of Unusual Distribution, ibid. **53**:125-127 (Feb.) 1946. McGuire, J. A., and Shaffer, B.: Fixed Bullous Eruption Due to Sulfathiazole, ibid. **52**:342-343 (Nov.-Dec.) 1945. Peterkin, G. A. G.: Brit. M. J. **2**:1-6 (July 7) 1945. Pérez Gil, J. L.: Arch. mex. ven. y dermat. **6**:153 (July-Aug) 1947. Grau, E. B.: Med. clin., Barcelona **7**:157-158 (Aug.) 1946. Freeman, H. E.: Fixed Eruption from Sulfadiazine or Sulfamerazine, Arch. Dermat. & Syph. **50**:45 (July) 1944. Dostrovski, A., and Sagher, F.: Fixed Erythema Due to Sulfanilamide with Gradually Lessening Sensitivity, ibid. **49**:418-420 (June) 1944. Director, W.: Fixed Eruption, Conjunctivitis and Fever from Sulfathiazole, ibid. **48**:523-524 (Nov.) 1943. Cornbleet, T.; Schorr, H., and Musgrave, D.: Transactions of the Chicago Dermatological Society, ibid. **61**:694 (April) 1950.

3. Brocq, L.: Éruption érythémato-pigmentée fixe due à l'antipyrine, Ann. de dermat. et syph. **5**:308, 1894.

a few days, leaving residual pigmentation. Four days preceding the patient's first visit to the clinic the lesion had flared, and at about the same time he had noticed itching on the glans penis.

Examination showed a round maculopapule measuring approximately 3 cm. in diameter on the left anterior portion of the thorax. The central portion of this lesion was of a brown to a violaceous hue, and this coloring tapered off in a concentric fashion through several shades of red to a pink periphery. On the dorsal surface of the glans penis was a violaceous oval lesion measuring 1 by 1.5 cm. in diameter. Its surface was slightly moist.



Fixed type eruption with bullous reaction produced by combisul® (case 2).

The patient had been a medical seaman and had taken sulfadiazine occasionally during a period of four or five years but had not associated ingestion of the drug with previous exacerbations of the lesion on his chest. He had taken sulfadiazine a few hours preceding his most recent flare.

Both lesions subsided within 36 hours after his first visit to the clinic. After they had remained quiescent for one week, the patient was given 1 Gm. of sulfadiazine. Within two hours there was itching and redness at both sites. The lesion on the chest was elevated and urticarial in appearance while that on the glans was moist and eroded. Ten days later both lesions were quiescent but there was residual hyperpigmentation.

CASE 2.—C. W. (#677880), a 26 year old Negro woman, was admitted to the Urology Service because of a urethral diverticulum and trigonitis. She was given combisul® (sulfadiazine, 0.166 Gm.; sulfamerazine, 0.166 Gm., and sulfathiazole, 0.166 Gm.) and within 24 hours itching and swelling appeared in several circumscribed areas of old pigmentation located on the lips, forearms, hands and legs. Approximately one year prior she had been treated in another hospital with one of the sulfonamides for the same type of urinary tract disease and had manifested for the first time urticaria-like pruritic lesions at the same sites as previously noted, which were followed by residual hyperpigmentation.

Examination showed elevated urticarial lesions on the lips, arms, hands and legs. These were superimposed on circular pigmented patches and were surrounded by an erythematous halo. As the lesions evolved they became bullous. Pruritus, which at first had been a prominent symptom, gave way to exquisite tenderness, and the lesions became more deeply infiltrated.

All cleared slowly after use of the sulfonamide was discontinued, leaving prominent patches of hyperpigmentation. Because of the severity of the reaction separate fractions of the combisul® were not readministered to test for the responsible sulfonamide.

CASE 3.—J. F., a 5 year old oriental boy, was first seen in the Dermatology Clinic because of a lesion on the right flank which had first appeared as a "hive" 18 months previously. With each febrile illness the lesion became swollen and pruritic; it persisted as a patch of pigmentation otherwise.

Questioning of the parents (the father was a physician and the mother a nurse) elicited the information that the child had routinely been given sulfadiazine for minor illnesses and that exacerbations of the lesion had coincided with administration of the drug.

Examination at the time of the first visit revealed a hyperpigmented circular plaque which measured 2.5 cm. in diameter on the right lumbar area. Centrally the color was deep brown, and this shaded to an erythematous border. The surface was excoriated and somewhat lichenified. An exacerbation was produced by administration of sulfadiazine.

ONYCHOTILLOMANIA

Case Report

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AND
MICHAEL J. SCOTT, M.D.
NEW YORK

Onychotillomania is an uncontrollable desire to pick or tear the nails, usually a manifestation of a compulsion neurosis. It is similar to, but to be differentiated from, onychophagia, the habit of biting the free edge of the nails. Either may result in pronounced nail deformities. The treatment of onychotillomania consists in psychotherapy and the application of occlusive dressings. A fairly extensive review of the literature in English fails to disclose a single recorded case of this disease. In the German literature, Alkiewicz [1] refers to the condition.

REPORT OF CASE

A 60 year old woman complained of progressive deformity of several finger and toe nails, of four years' duration. The condition initially involved the nail of the right third finger; subsequently other finger and toe nails were affected. The use of finger nail polish was denied. Incidentally, the patient was left handed. Otherwise the history was noncontributory.

1. Alkiewicz, J.: Über Onychotillomanie, Dermat. Wchnschr. **98**:519-521 (April 28) 1934.

Fig. 1.—The condition observed on the right hand of a left-handed person with onychotillomania.

Fig. 2.—The condition as seen on both thumbs of a person with onychotillomania.

Physical examination disclosed no pathological observations other than the affected nails. The nail plates of the first, third and fifth digits of the right hand; of the first, third and fourth digits of the right foot and of the first digit of the left foot were involved. The lateral aspects of these nails appeared to have been forcibly torn away in varying degree. In some the nail bed was exposed. The nail plates were not discolored. Some nails showed subungual hematomas.

The distribution and bizarre appearance of the affected nail plates made one suspect a traumatic etiology. On direct questioning the patient admitted tearing away portions of the nails and nail beds. She claimed that she was merely dissecting and removing tissue which had been destroyed by "minute organisms." She stated that she could observe and isolate these organisms. After a rather diligent search she proudly exhibited a barely visible black particle. This inert specimen possessed all the physical properties of soot. Direct and cultural examinations of material obtained from the affected nails were negative for fungi, and an intracutaneous trichophytin test elicited negative reactions. Superficial attempts to discover the underlying causative psychologic factors were unsuccessful. Occlusive dressings were applied with encouraging results, but psychiatric evaluation will undoubtedly be necessary before permanent cure can be achieved.

FAMILIAL LICHEN PLANUS

Report of Three Cases in One Family

DARIO ARGUELLES-CASALS, M.D.
HABANA, CUBA

The occurrence of lichen planus in three members of one family is of sufficient rarity and interest to warrant reporting.

REPORT OF CASES

CASE 1.—M. R., a white woman aged 38, consulted me in June 1941 for an eruption on the legs, arms and trunk. The lesions were of the chronic variety of lichen planus. No other lesions were found. Pruritus was intense.

CASE 2.—E. R., the 36 year old sister of M. R., consulted me in December 1947 for an eruption which had been present for three years. Examination revealed typical lichen planus on both axillas and the chest area. Pruritus in this case was intense.

CASE 3.—C. P., aged 63, mother of M. R. and E. R., consulted me in December 1947 for a widespread eruption of lichen planus. The lesions involved the legs, thighs, arms, chest and the back of the hands. Severe pruritus required local x-ray therapy.

COMMENT

Familial lichen planus is rare. Saffron reported four cases of lichen planus in one family in 1940, compiling a total of 60 reported cases, 50 of the consanguineous variety and 10 of the conjugal type. These observations are of interest because they may give an etiologic clue. It seems to me that the observation in my report favors a familial disposition.

News and Comment

GENERAL NEWS

Prizes Awarded in First Annual Essay Contest of American Dermatological Association.—Close competition marked the first annual prize essay contest sponsored by the American Dermatological Association to stimulate younger investigators to original work in the fields of dermatology and syphilology. A total of 15 manuscripts was submitted to the Research Aid Committee of the Association, which based its decisions on the following considerations: (1) originality of ideas, (2) potential importance of the work, (3) experimental methods and use of controls, (4) evaluation of results, (5) clarity of presentation, (6) historical background and (7) bibliography.

The high quality of the theses made it difficult to arrange them in order of merit. In the opinion of the judges, only a few points separated the three outstanding contributions.

A special award of honorable mention is therefore given to S. William Becker, Jr. for his paper on "The Dendritic Cell of the Epidermis" and to Joseph W. Goldzieher for his paper on "'Chemical' Analysis of the Intact Skin by Reflectance Spectrophotometry."

The winner of the first prize is Thomas B. Fitzpatrick. His thesis is entitled "The Tyrosinase Reaction as a Specific Index of Malignancy of Pigment Cell Neoplasms, With Particular Reference to Malignant Melanoma."

Dr. Fitzpatrick will receive a cash award of $300 as well as an invitation to present his thesis at the seventy-fifth anniversary meeting of the American Dermatological Association, to be held at The Homestead, Hot Springs, Va., May 23 to 26, 1951.

The sponsors of this project are encouraged by the number who participated, and they extend heartiest congratulations to the winners. Details of the next contest will be forthcoming soon.

First Earl D. Osborne Fellowship Awarded.—Dr. Victor C. Hackney of Indianapolis has received the appointment as the first annual Earl D. Osborne Fellow in Dermal Pathology at the Armed Forces Institute of Pathology, starting July 1, 1951. This Fellowship is sponsored by the American Academy of Dermatology and Syphilology.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Maurice J. Costello, M.D., *Chairman*
Wilbert Sachs, M.D., *Secretary*
Feb. 7, 1950

Keratosis Blennorrhagica. Presented by Dr. F. Philip Lowenfish.

G. W., a Negro aged *27*, is presented from City Hospital with a painful swelling of all joints, associated with fever, and an eruption on the scalp and feet of seven years' duration, with an acute exacerbation for the past two months.

Seven years ago the patient noted painful swelling of the ankles, which slowly progressed to involve all the joints. Four years ago a vesicular eruption appeared on the soles, with a resulting thick crust formation that has continued to the present. During the current exacerbation subungual areas of the middle fingers have also become involved.

In January 1947 the patient was admitted to Sydenham Hospital, where a diagnosis of gonorrheal urethritis, prostatitis, arthritis and acute iritis was made. Treatment consisted in nonspecific protein therapy and administration of sulfadiazine. The arthritis and the urethritis improved. Use of atropine and penicillin ointment slowly cleared the iritis. In December 1947 the patient was admitted to Columbia Hospital, Columbia, S. C., where he was treated for acute arthritis, probably gonorrheal. He was given 800,000 units of penicillin and showed some improvement. The patient was admitted to City Hospital on Dec. 14, 1949. He denied gonorrheal infection, but according to the records of other hospitals he had admitted that such infection was present seven years ago.

Examination showed an acutely and chronically ill, undernourished Negro with fusiform swelling of the interphalangeal joints, painful swelling of the wrists, elbows, ankles, knees and hips, "poker" back and inability to move any joints without experiencing severe pain. There was pronounced subungual hyperkeratosis of the middle fingers. The weight-bearing surface of the feet was covered with hyperkeratotic plaques with well defined margins. The scalp showed a like involvement. Lateral nystagmus was present. The prostate was enlarged, soft and tender.

The Mazzini reaction was negative. Results of urinalysis were normal. Examination of the blood showed 12 Gm. of hemoglobin, 2.8 Gm. of albumin and 2.9 Gm. of globulin per 100 cc. An electrocardiogram revealed only tachycardia. A prostatic smear on admission contained gram-negative and gram-positive diplococci. (No gram-negative diplococci are seen in the prostatic smears at present.) A culture for gonococcus showed no growth. Roentgenograms of the fingers, wrists, elbows, neck, knees and ankles showed osteoporosis, periarticular swelling and narrowing of the joint spaces. The spine showed changes suggestive of Marie-Strumpell disease.

Biopsy of skin from the foot disclosed massive hyperkeratosis and parakeratosis. Just above the region of the granular layer the epithelial cells were vacuolated. They were large and separated by numerous polymorphonuclear leukocytes. In general the epidermis was edematous. The morphologic picture was felt to be such as is seen in keratosis blennorrhagica, but in view of the sections from the scalp it was thought that a definite diagnosis of this disease could not be made. Sections stained with the Gram technic disclosed gram-negative granules which, however, it would have been hazardous to interpret as being Neisseria gonorrheae.

Biopsy of a specimen from the back showed localized acanthosis and hyperpigmentation of the epidermis. In one or two locations at the apexes of papillae the superficial epidermal strata contained aggregates of polymorphonuclear leukocytes. Numerous chromatophores were seen within the papillary bodies.

Sections from the scalp disclosed epidermis which had undergone remarkable acanthosis. The rete pegs were exceedingly long, as were also the papillary bodies. The granular layer was for the most part retained. The more superficial layers were represented by a massive band of compact parakeratosis which contained a few polymorphonuclear leukocytes. The papillary part of the cutis was the site of a mild chronic inflammatory reaction. There were many chromatophores. From the histologic picture the pathologist believed it was still a moot question whether the disorder could be considered a case of keratosis blennorrhagica or pustular psoriasis complicated by arthropathy.

Treatment has consisted in the administration of vitamin A, 50,000 units three times a day, and procaine penicillin with aluminum monostearate, 600,000 units daily for 10 days; the application of hydrous wool fat (lanolin) dressings to the feet; a daily wash and shampoo of the hair and scalp, and the use of codeine and acetylsalicylic acid to control the arthritic pain.

The arthritis is symptomatically and clinically improved. The thick keratotic scales of the feet have become considerably lessened. The patient has lost the nails of the middle fingers and the hyperkeratotic plaques with them. The prostate is now small, fibrotic and nontender. Since removal of tissue for biopsy was done two weeks ago in the midline of the lower part of the back, keratotic, discrete, papular lesions have appeared in this area.

The ophthalmologist considers the nystagmus to be congenital.

DISCUSSION

DR. LOUIS CHARGIN: It is more than likely that we are dealing with psoriasis arthropathica rather than keratosis blennorrhagica. The eruption, which is psoriasiform, is located on the ends of the fingers; the small joints are involved, and there are none of the characteristic waxy papules seen in keratosis. Moreover, the scalp lesions resemble psoriasis. There is no history or definite evidence warranting the statement that the patient had gonorrhea.

DR. PAUL GROSS: I suggest the diagnosis of Reiter's disease, and the history of previous involvement of the eyes is particularly in favor of that diagnosis. I agree with Dr. Chargin that cases of so-called chronic keratosis blennorrhagica with negative bacteriologic findings are nothing else but psoriasis arthropathica. Reiter's disease with cutaneous lesions and psoriasis arthropathica may resemble each other a great deal, and both are complicated by polyarthritis. Gonorrhea usually results in a monoarthritis and involves the large joints.

DR. A. BENSON CANNON: † The lesions were chiefly confined to the soles and the dorsum. of the toes. Some had thick, crusted areas. Along the outer borders were distinct corps ronds type plaques. There were few lesions on the hands, and these were on the dorsa of the ends of the fingers. There was even crusting in some of the affected areas of the scalp, which would easily fit in with the diagnosis of keratosis blennorrhagica. The patient had a history of gonorrhea and was treated in three different hospitals for gonorrhea and gonorrheal arthritis. Gonococci were demonstrated in smears taken from the urethra and prostate. Arthritis was present not only in the finger joints but also in the knees, ankles and wrists.

Leprosy. Presented by DR. J. LOWRY MILLER.

B. O., a Puerto Rican man aged 22, was admitted to City Hospital on Jan. 9, 1950 because of acute arthritis, hyperpyrexia and a cutaneous eruption, of one week's duration. The onset was characterized by painful swelling of the joints of the extremities, shortly followed by fever and a generalized erythema-multiforme-like eruption most evident on the face and extremities.

The patient had enjoyed good health except for a similar but somewhat severer episode, for which he was hospitalized, five years previously in Puerto Rico. The diagnosis at that time was nephritis and urticaria. The illness subsided in about one month.

On admission the patient was acutely ill, with a temperature of 101.8 F. There were erythematous, tender, indurated, scaling macules, which blanched on diascopic pressure, on the face and chest and to a lesser extent on the trunk. They were most numerous on the extremities and tended to coalesce, giving the appearance of inverted horseshoes. On the ears there were

† Dr. Cannon died on Nov. 27, 1950.

discrete, erythematous, scaling and indurated nodules. The joints of the extremities were hot, painful and swollen. Generalized lymphadenopathy was present. The greater auricular, ulnar and radial nerves felt cordlike. There was no demonstrable change in sensation to pinprick, heat and cold or touch.

The Mazzini reaction of the blood was negative. Urinalysis on admission showed albumin, cellular granular and hyalin casts, red blood cells and a few white blood cells. Recently the urine has been normal. The white blood cells on admission ranged from 35,000 to 43,000, with 89 polymorphonuclear leukocytes and 8 lymphocytes. At present the white blood cells are 12,300, with 57 polymorphonuclear leukocytes, 37 lymphocytes and 4 monocytes. The sternal marrow showed myelogenous hyperplasia. The hemoglobin was 11 Gm. per 100 cc.; red blood cells, 5,400,000; blood sugar, 75 mg. per 100 cc.; blood urea nitrogen, 19.8 mg. per 100 cc.; albumin, 3.1 Gm. per 100 cc., and globulin, 3.2 Gm. per 100 cc. Roentgenograms of the chest and hands were normal. Smears from scrapings of the cut surface of a nodule on the ear showed numerous acid-fast organisms typical of Hansen's bacilli. No acid-fast organisms were found in smears from the mucous membranes of the nose. Biopsy from a macule on the right arm disclosed changes "almost certainly due to leprosy which shows minimal reactivity." A biopsy specimen from the ear lobe was diagnosed as revealing "an interesting example of a so-called lepra reaction."

During the first four days in the hospital the patient appeared acutely ill, but on the fifth day there was dramatic spontaneous improvement. Joint swelling and pain receded, and the temperature returned to normal. The cutaneous lesions began to scale and subside, leaving the shiny appearance now seen. At present the ears show more erythema and scaling after the initial improvement. Neurologic examination showed hypesthesia in the involved areas.

Medication in the hospital consisted in the administration of codeine, acetylsalicylic acid, multiple vitamins and crude liver parenterally.

DISCUSSION

DR. FREDERICK REISS: This case shows rather peculiar but quite well known features. The diffuse infiltration of both ear lobules probably harbors many bacilli. This condition is peculiar, because the face, except for a small patch, doesn't show any diffuse infiltration of a lepromatous nature, which one would expect in such a case. The second interesting feature is the thickened ulnar nerves without sensory disturbance. This is quite well known in lepromatous leprosy, for only the perineural sheaths are affected, with no degeneration of the nerve as such. If a specimen were excised it would reveal typical lepromatous infiltration similar to that of the ear lobules. The third interesting feature is the lepra reaction. Leukocytosis and eosinophilia are often reported but are not necessarily present in the typical erythema multiforme reaction. This is known to occur rarely spontaneously but often during treatment. I think that in this instance intensive treatment would provoke a lepra reaction. It would be interesting to perform a lepromin test at this point. I am almost certain that the reaction would be negative. The lepra reaction itself is often considered allergic, but it is not comparable with the Jarisch-Herxheimer reaction; that is, it is more or less a toxic rather than an allergic manifestation.

DR. CHARLES WOLF: Since the patient is showing rather malignant manifestations of the disease I would suggest the use of diaminodiphenyl sulfone, which the British have perfected. They claim fine therapeutic results with fewer side reactions than encountered with other members of the sulfone group.

DR. J. LOWRY MILLER: We thought this case was particularly interesting because the man gives the history of an exactly similar episode five years ago in Puerto Rico, with an erythema-multiforme-like eruption, fever and arthritis, which at that time was diagnosed as urticaria and nephritis. We found no evidence of nephritis this time. The patient had apparently gone along well for five years until this acute outbreak developed. We think the prognosis is good in this case since the man is acquiring his own resistance, and we feel that treatment must be given cautiously because it may do him more harm than good. He is already manifesting a lepromatous reaction from diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) therapy. We will be glad to follow Dr. Wolf's suggestion.

Leukoderma (Due to Contact with Rubber). Presented by DR. LEO SCHWEICH.

V. P., a Negro woman aged 43, is presented from the Vanderbilt Clinic. During the summer of 1949 she wore the following garments containing rubber: (*a*) a girdle, of which the two main sections were made of a rubberized material; (*b*) an apron, made of rubberized material and kept in place by a rubberized neck band, and (*c*) beach sandals which were held in place with straps across the insteps, made of a similar material.

About a month later she noticed a gradual loss of pigment in the areas which came into direct contact with these materials. This was accompanied with mild itching in the areas covered by the girdle; an eruption was not noticed at any time. During the succeeding weeks the involved areas lost their pigmentation almost completely.

On December 29, when the patient was first seen at the clinic, she presented well demarcated depigmented patches in all areas where the skin came into direct contact with the articles named: (*a*) Around and below the waistline there was almost complete depigmentation. The pigment in this area was preserved only in the form of narrow stripes where the rubberized parts of the girdle were held together by cotton or rayon material. (*b*) The upper part of the chest and neck showed many depigmented areas of varying sizes. (*c*) On the dorsa of both feet were less sharply defined areas of depigmentation.

No cutaneous symptoms, subjective or objective, were present at that time.

Serologic tests for syphilis gave negative reactions, and results of urinalysis were normal. Examinations for fungi were negative. Patch tests with the original materials could not be performed as the patient had disposed of all garments concerned.

On the patient's subsequent visits to the clinic during January the gradual reappearance of pigment was noted in almost all the areas involved, chiefly along the margins, giving them a mottled appearance. The only areas which still show activity and in which depigmentation has increased during the past few weeks are located on the thighs and correspond to the position of four rubberized garter buckles.

DISCUSSION

DR. GEORGE M. LEWIS: I should like to ask the presenter whether the return of pigment in leukoderma is always follicular at first, as in this case.

DR. EUGENE T. BERNSTEIN: This is a self-limited disorder; the pigment will return, and there will be no sequelae. This depigmentation was photographic, so that every part of the garment was reproduced and the skin not coming into contact with it was normal. I had one case in a white person, whose skin turned black but also later became normal.

DR. LEO SCHWEICH: I presented this case especially for these reasons: First, the leukoderma appeared in three separate and distant areas, caused by three different objects of clothing, at the same time and in the same person. Second, this case confirms the opinion of most observers that depigmentation is the only symptom caused by the contactant, without any preceding visible cutaneous eruption. Third, it also shows that a direct and prolonged contact is required for these characteristic lesions. No similar patches were observed in distant location; as a matter of fact, the original pigmentation was preserved completely even within the patches of leukoderma in those areas where the skin was prevented from coming into immediate contact with the rubber.

Although patch tests could not be performed with the original material, the patient unwittingly performed her own tests. She bought a girdle which did not consist of rubber or rubberized material, but she overlooked the fact that there were garters on each side which did contain rubber, and the areas which came into contact with the garters are the only areas which still show activity, with no return of pigment. In the other lesions the pigment returned spontaneously but slowly, chiefly from the margins. We tried to hasten repigmentation in some areas by application of ultraviolet irradiation and in other areas by heat. Although the time of observation has been too short, we do not think these treatments were of much benefit. As Dr. Bernstein says, the prognosis is "favorable," but it often takes a long time for the pigment to return.

An article was published in *The Journal of the Royal Egyptian Medical Association* about a year ago reporting the successful treatment of vitiligo by the oral use of a photosensitizer together with ultraviolet therapy. Although vitiligo and leukoderma due to contact are different

conditions etiologically, their common denominator is the lack of pigment, and the present type of leukoderma might be benefited by the same treatment. Dr. Sekla of Cairo, who is in this country with the United Nations World Health Organization, is at this meeting and I am sure would say a few words on this subject.

Dr. Magdi Sekla, Cairo, Egypt (by invitation): Extensive studies on ordinary vitiligo have been carried on with extracts of a plant called Ammi majus, known from olden times. The extracts consist of two alkaloids (ammoidin and ammidin). Pharmacologic and clinical studies have been mainly performed at Fuad University, Cairo, where alcoholic extracts of the plant were first tried in oral doses as well as by application on the leukodermic areas. At first, always from impurities in the crude plant, there were toxic effects consisting in nausea, vomiting, diarrhea and severe vesiculation and bulla formation in the affected areas, but now toxic symptoms are no longer encountered and the pure extracts, combining the two alkaloids, are prepared in tablet form. They are given in doses of two 0.5 Gm. tablets three times daily for one to two months, in conjunction with ultraviolet irradiation once a week. The patches of vitiligo disappear completely during this period, showing at first erythema and slight edema before repigmentation. No tendency to recurrence has yet been observed. Articles on the subject were published in *The Journal of the Royal Egyptian Medical Association* in 1948, and the experiments are still being carried on with hundreds of patients. Results are very promising.

Nutritional Neuropathy. Presented by Dr. A. Benson Cannon.
Lymphosarcoma. Presented by Dr. Gerald F. Machacek.

NEW YORK DERMATOLOGICAL SOCIETY

John C. Graham, M.D., *President*
Anthony C. Cipollaro, M.D., *Secretary*
Feb. 28, 1950

Actinomycosis. Presented by Dr. A. Benson Cannon.†

J. M., a woman aged 21, was previously presented at the January meeting. All lesions are now healed, with the exception of a granulating area on the right cheek 1 cm. in diameter. Treatment, which continues, has consisted in the following: (1) penicillin—46 daily injections to date, beginning with 600,000 units and gradually increasing (The last 27 injections have consisted of 1,800,000 each, for a total so far of 65,700,000 units [January 12 to the present]); (2) sulfadiazine—4 Gm. daily for six days (January 15 to 21), discontinued because of nausea; (3) aureomycin—2 capsules four times daily for four days (January 22 to 26), discontinued because of nausea and gas; (4) chloramphenicol (chloromycetin®)—2 capsules four times daily for 15 days (January 26 to February 9), discontinued because of low grade fever; (5) sodium iodide—1 Gm. intravenously daily for 12 days (January 26 to February 7), and (6) local therapy—daily cleansing of wounds with hydrogen peroxide and liquid synol® soap, swabbing of ulcers and cavities with 50 per cent phenol, cauterization of excessive granulation with 25 per cent silver nitrate and application of streptomycin dressings, changed to thymol iodide powder 10 days ago when discharge had ceased.

Note.—The remaining lesion subsequently healed completely, with inconspicuous scarring. A total of 150,000,000 units of penicillin was given. There had been no recurrence during 11 months' observation.

DISCUSSION

Dr. George M. Lewis: The clinical picture, when the patient was seen last month, was such that I don't think anyone could have been certain the condition was actinomycosis. However, not only has the organism been demonstrated very beautifully but also Dr. Cannon has achieved substantial improvement of the patient on treatment with penicillin, and the combination of events has convinced me that the diagnosis of actinomycosis is correct. The one item that is still unexplained is why granules have not been found. Although there have been cases in which they have not been demonstrated it is still unusual not to find them in a well worked-up case.

† Dr. Cannon died on Nov. 27, 1950.

The causative organism produces granules in the tissue, and the fact that there have been no granules in the pus makes it extremely difficult for one to arrive at the diagnosis.

DR. FRANCESCO RONCHESE, Providence, R. I. (by invitation): I recall another instance in which no granules were demonstrated.

DR. MAURICE J. COSTELLO: There are extremely few after-effects for such extensive involvement.

MRS. E. L. SCHNALL (by invitation): I have been combing the literature on actinomycosis and was surprised to see how frequently it is mentioned that it is not unusual not to find "sulfur granules." Rosebury, in four cases of the cervicofacial type, in each of which Actinomyces bovis was isolated, found granules in the pus in only one. In the second case branching, gram-positive rods were seen on direct examination of the pus. The other two cases revealed no organisms on direct examination. Zachary Cope, in his work "Actinomycosis," makes reference to the fact that the granules frequently are not found. In the Conant and Rosebury chapter on "The Actinomycetes" in Dubos' "Bacterial and Mycotic Infections of Man," the point is again made about not finding the granules readily. Also, the patient in the present case came to Dr. Cannon rather late after the onset of the disease and had received previous medication which might have contributed toward the lack of granules in the material. Whatever treatment she had received might have been enough to keep down the infection sufficiently to prevent the demonstration of the organism in the direct preparations.

DR. GEORGE M. LEWIS: The fact that we don't find granules makes it difficult to tie up the cultures with the case in hand. There is no sure way of saying that the organism is responsible for the pathologic condition and is not incidental.

MRS. E. L. SCHNALL (by invitation): I don't know of any actinomycete that is a gram-positive, branching, non-acid-fast anaerobe other than A. bovis.

DR. GEORGE M. LEWIS: Finding actinomycetes in material from these open lesions doesn't exclude the possibility that they are saprophytes. Pathogenicity is not established by mere isolation of the organism. Actually, that isn't proof. This point is what makes the case interesting. It is still unusual not to find granules in a case which is carefully studied, provided that a species of Nocardia is not responsible.

DR. A. BENSON CANNON: Dr. Elizabeth Hazen, who has had great experience in mycology in the New York State Health Department, told us of two cases in which actinomycetes were not found for at least six months and of still a third in which the disease was not diagnosed until autopsy, at which time actinomycetes were found. I think these observations stress the point that Dr. Lewis and others have brought out, that it is sometimes exceedingly difficult to make a diagnosis of actinomycosis, both clinically and from a laboratory standpoint. Apparently, the best results would come from a combination of clinical and laboratory studies. I don't think you can altogether ignore the results of treatment, which also indicate that the condition was actinomycosis.

Subacute Lupus Erythematosus: Psoriasis. Presented by DR. ANTHONY C. CIPOLLARO.

G. C., a woman aged 34, consulted me on Feb. 17, 1950 for treatment of an eruption of the face, ears, chest, upper extremities and mouth. The patient stated that two "spots" had appeared on the nose seven years before, for which lesions she had received gold injections. Two years ago an eruption had recurred on the face and also involved the arms. Treatment consisted in the administration of liver, bismuth sodium triglycollamate (bistrimate), gold, lextron® (a proprietary liver-stomach concentrate with iron and vitamin B complex), penicillin, tocopherols and quinine. The patient stated she also had had psoriasis for 18 years and had been treated with x-ray irradiation to the elbows and occiput, but with no benefit.

The patient presents discoid, erythematous, scaly, atrophic and telangiectatic lesions, some with follicular plugging, on the face, arms, forearms, sides of the neck and the chest. The ears are erythematous, edematous and tender, with scaling. Erythematous scaly papules are present on the elbows and occiput. The distal interphalangeal joints of the fingers are swollen and red. Hemorrhagic and telangiectatic areas are present on the buccal mucosa.

The blood count showed mild leukopenia with a normal differential count and normal erythrocyte sedimentation rate.

Biopsy of a lesion of the arm revealed no evidence of psoriasis. The histologic observations were suggestive of lichen planus more than of lupus erythematosus. The clinical picture of the facial lesions is that of lupus erythematosus and of the chest lesions is that of psoriasis.

DISCUSSION

DR. LESLIE P. BARKER: The distribution, type of scaling and color of the lesions with resultant scarring in some areas would favor a diagnosis of lupus erythematosus. The fact that a similar eruption cleared a few years ago after gold therapy would help substantiate this diagnosis.

DR. WILBERT SACHS: It is possible that this patient did have psoriasis, but clinically I would call the condition lupus erythematosus tonight, especially since there are lesions in the mouth and because of the distribution and type of lesions on the face. The sections showed no evidence of psoriasis. The picture was typical of lupus erythematosus, but I couldn't understand the lack of elastic tissue and basophilic degeneration in a long-standing case of lupus erythematosus. On the other hand, the condition did have features of lichen planus, and I didn't know which one to call it. Clinically, I would call it lupus erythematosus. Microscopically there are features for and against both that disease and lichen planus.

DR. GEORGE C. ANDREWS: I agree that it is a case of lupus erythematosus. The question is how it should be classified—whether it should be called the disseminate subacute type or the disseminate discoid type. It has lasted six years without much change, and the lack of systemic symptoms suggests the disseminated discoid variety. Some of the lesions would show better under ultraviolet radiation. There is puffiness and telangiectasia of the tips of the fingers. I think conservative gold preparation therapy would be best.

DR. MAURICE J. COSTELLO: This woman was a patient of mine about nine or 10 years ago. At that time she had lesions on the elbows that I thought were characteristic of psoriasis and lesions on the face which I thought characteristic of lupus erythematosus. I and others have presented patients with both diseases. When I administered a gold preparation intravenously, all lesions on the face completely disappeared. This evening I think she has the psoriasiform type of discoid lupus erythematosus.

DR. GEORGE M. LEWIS: A case of this type always presents difficulties from the standpoint of prognosis. Is the diagnosis discoid disseminate lupus erythematosus or subacute disseminated lupus erythematosus? From the evidence presented tonight, I believe that the rash is of the discoid disseminate type, but the boundary line between that and the subacute type is very narrow, and we have to be cautious in treatment. Gold therapy should be pursued very carefully, with minimal doses slowly increased. The latest work on lupus erythematosus shows that the discoid variety is not always a disease of the skin alone.

DR. A. BENSON CANNON: I agree with previous speakers that the lesions resemble lupus erythematosus subacutus disseminatus, but I should not lose sight of the possibility of lymphoblastoma. The long duration of the disease, the infiltration and bluish red color of the lesions, the itching and the failure of microscopic study to show the presence of either lupus erythematosus or psoriasis, with resemblance to the picture seen in lichen planus, led me to suspect the possibility of lymphoblastoma. We have all seen cases of psoriasis and lichen planus eventually terminate in mycosis fungoides. I should suggest that the patient be hospitalized and thoroughly examined before any form of treatment is given.

DR. FRANCESCO RONCHESE, Providence, R. I. (by invitation): I agree with the diagnosis of chronic disseminated lupus erythematosus. An interesting feature was the keratotic lesion on the palmar aspect of one thumb and the separation of two nails, as usually seen in psoriasis.

DR. FRANCO FLARER, Padua, Italy (by invitation): I accept Dr. Cipollaro's diagnosis clinically, but histologically the condition shows only nonspecific features of vascular inflammation.

DR. FRANK E. CORMIA: The presence of psoriasis along with another disease may influence the character of that disease. Like Dr. Costello, I have occasionally seen patients with both

lupus erythematosus and psoriasis. Recently one of my patients with chronic psoriasis manifested lesions of subacute lupus erythematosus in different areas. After therapy of a focus of infection in the genitourinary tract with chloramphenicol (chloromycetin®), new lesions of lupus erythematosus appeared; coincidentally the psoriatic lesions assumed a different character and became clinically indistinguishable from those of the lupus erythematosus. Biopsy revealed a toxic dermatitis; neither psoriasis nor lupus erythematosus could be identified.

DR. ANTHONY C. CIPOLLARO: This girl did have psoriasis; several dermatologists made that diagnosis before dissemination of the lupus erythematosus occurred. Dr. Costello made it before she had as many lesions as she now shows. At present there is some evidence of psoriasis —scaly patches in the scalp without alopecia, and changes in some of the nails. This certainly isn't an ordinary case of disseminated discoid lupus erythematosus or even subacute lupus erythematosus. It has features which are different from either, and because of these I made a biopsy, which didn't help much because the histological picture was as confusing as the clinical picture. I am inclined to feel as Dr. Cannon does, that this disease may change into something different from what we are talking about tonight.

A Case for Diagnosis: Calcinosis Cutis Circumscripta? Presented by DR. GEORGE M. LEWIS.

P. C., a man aged 48, noticed about nine or 10 months ago some small, hard plaques under the skin of the shaft of the penis. In about one month they had coalesced and attained a size nearly equal to their present one. No symptoms have been noted except that with erection of the penis there is an exaggerated dorsal curve. The past history is noncontributory except for a history of calcium injections as a "spring tonic" for the past few years. There has been no localized trauma.

On the dorsal and ventral surfaces of the midshaft of the penis there are palpable two subcutaneous, firm, nontender, flat, polygonal plaques measuring about 2 by 2 cm. These appear to be partially attached to the underlying structures but not attached to the overlying skin.

Treatment has consisted in injections of vitamin D and ascorbic acid and the administration of iodides by mouth and by injection. Neither enlargement nor regression of the lesions has been noticed while the patient has been under treatment.

The patient's general health has been good.

DISCUSSION

DR. GEORGE C. ANDREWS: I think the condition is rather typical induratio plastica penis, which is often associated with lichen sclerosus et atrophicus, or Dupuytren's contracture. Treatment with vitamin E is supposed to cure it.

DR. A. BENSON CANNON: I agree with Dr. Andrews, although I have seen benefit only from surgical excision.

DR. FRANCESCO RONCHESE, Providence, R. I. (by invitation): Did the patient have the other parts of the syndrome?

DR. GEORGE M. LEWIS: There are a few pinhead-sized areas of atrophy across the shoulders.

DR. FRANCO FLARER, Padua, Italy (by invitation): The Frei reaction is positive in some of these cases.

DR. FRANK E. CORMIA: Did the patients with positive Frei reactions have improvement with therapy?

DR. FRANCO FLARER, Padua, Italy (by invitation): Yes, we had two such cases.

Ulcer (Cause?); Hodgkin's Disease. Presented by DR. GEORGE M. LEWIS.
Erythema Multiforme. Presented by DR. EUGENE F. TRAUB.
Mycosis Fungoides. Presented by DR. GEORGE M. LEWIS.
Pityriasis Rosea. Presented by DR. EUGENE F. TRAUB.
Keratosis Palmaris et Plantaris. Presented by DR. EUGENE F. TRAUB.
Subacute Lupus Erythematosus. Presented by DR. J. LOWRY MILLER.
Nevus Pigmentosus. Presented by DR. ANTHONY C. CIPOLLARO.

John C. Graham, M.D., *President*
Anthony C. Cipollaro, M.D., *Secretary*
March 28, 1950

Melanoma. Presented by DR. PAUL E. BECHET.

G. L., a man aged 34, noticed five years ago for the first time a lentil-sized black lesion on the upper right side of his chest, near the clavicle. This lesion has been growing rapidly for about 18 months and now presents a raised, blue-black, nonverrucous surface with a somewhat digitate outline at its periphery, rectangular in outline and about 40 mm. in diameter. While the patient has a few small ordinary pigmented nevi scattered over the body, they do not resemble the lesion in question. Fifteen x-ray treatments were administered by a radiologist, without benefit.

DISCUSSION

DR. A. BENSON CANNON: † I am by no means certain that the diagnosis of melanoma is the correct one. The lesion is said to have begun as a mole in early life and began to grow only during the last year and a half. It is not large, is superficial and is composed of multiple small papules varying from light tan to dark brown to slate color. It may be one of a number of things, such as blue nevus, junction nevus or a true melanoma. Biopsy reports in such cases are oftentimes difficult to interpret; however, I should be guided in my treatment by the results of histopathologic examination. Probably excision or coagulation would be the most desirable method of removal. I am inclined to believe that the prognosis is good.

DR. GEORGE C. ANDREWS: I think the lesion is a melanoma. There are satellite lesions present. The patient didn't notice a preceding mole and doesn't know just when the lesion started. It should be excised or treated by electrocoagulation.

DR. ANTHONY C. CIPOLLARO: The two previous speakers have covered all the essential points. It is a question of how much to remove. I would be inclined to destroy the lesion completely by wide electrocutting or scapel excision and let it go at that. In my opinion, more radical surgery is not now indicated.

DR. GEORGE M. LEWIS: Dermatologists might well pool their cases in a skin cancer registry and from time to time analyze the records of all patients with cutaneous cancer that they treat. There would then be statistical proof, I am sure, for the conservative attitude in which we believe. The disarticulation of limbs and extensive lymph node dissections rarely prolong life in patients with rapidly growing melanocarcinoma.

DR. WILBERT SACHS: This lesion may not be a junction nevus but one of many different dermatoses, including a blue nevus. Should it be a junction nevus, it may or may not be malignant. I believe biopsy of a small specimen would give considerable information as to the diagnosis and also would indicate proper therapy. I cannot understand how a nevocarcinoma could have been growing for a year and a half without more serious results.

Anaplastic Epithelioma in a Patient with Acrodermatitis Chronica Atrophicans. Presented by DR. GEORGE M. LEWIS and DR. WILBERT SACHS.

L. L., a woman aged 60, is presented from New York Hospital complaining of acrodermatitis chronica atrophicans of both legs, of nine years' duration, and an ulcer of the right ankle and heel, of about seven years' duration.

The patient was first seen by us in April 1948, at which time she had had acrodermatitis chronica atrophicans for seven years. About four months prior to this first visit she had manifested an ulcer of the right leg which did not respond to soothing medication and supportive bandages. She had had rather extensive varicose veins for 10 years, involving both legs, and these had been treated with sclerosing solutions. Chronic swelling of the ankles had been present for about the same period.

The patient was treated with conservative measures (ammoniated mercury ointment) for several months without much improvement. Because of the firm, granulomatous, elevated

† Dr. Cannon died on Nov. 27, 1950.

border of the ulcer, a biopsy was performed on Sept. 24, 1948. This revealed only granulation tissue, with no evidence of epithelioma. The patient was treated with three x-ray exposures of 75 r each during the next two months, without any improvement. She was then lost from observation for more than a year and was treated during that time with injections for varicose veins by a local physician. She claims that the ulcer of the right leg has become larger and more fungating in appearance during recent months. She returned to New York Hospital on Feb. 27, 1950, at which time another biopsy was performed because of the extensive and suspicious character of the lesion. The picture was reported as that of anaplastic epithelioma, and a second biopsy two weeks later from other areas also revealed anaplastic epithelioma.

On the right heel and ankle there is a large, fungating, ulcerative lesion about 3 inches (7.5 cm.) in diameter. The edges are firm, elevated and irregular, and the base is necrotic and deeply situated. There is no involvement of the regional lymph nodes. Typical extensive acrodermatitis chronica atrophicans is evident on both legs.

The Kline reaction of the blood was negative.

Biopsy showed that the epidermis in some areas was tremendously acanthotic with downward projection of the rete pegs. On one end of the section there was a rather wild acanthosis with loss of prickles and of the basal cell margin. The cells varied greatly in size, and some of the nuclei were abnormally large. There were increased mitosis and evidence of amitotic division. The upper part of the cutis was rather densely infiltrated with small round cells and wandering connective tissue cells and plasma cells.

DISCUSSION

DR. HOWARD FOX: This is the first case of this disease I have seen in which carcinoma developed.

DR. MAURICE J. COSTELLO: I agree with the diagnosis and the fact that epithelioma has developed. We have collected cases of this disease in which general practitioners or persons who treat peripheral vascular disorders have injected sclerosing solutions into the veins because they thought the patients had varicose veins, with severe reactions causing ulcerations which take a long time to heal. In this instance I think the epithelioma might never have developed if a sclerosing solution had not been used.

DR. GEORGE M. LEWIS: I think the finding of anaplastic cells precludes the use of x-rays, and the question comes up whether dermatologists should treat this case or refer it to the surgeons.

DR. EUGENE F. TRAUB: It depends a little on how the rest of the skin looks. I don't know whether there is any area where you could get a piece of skin that would do well for grafting or whether you would have to use small Thiersch grafts. If you could not get an area of skin that would take, I believe the dermatologists would do just as well with the electrocutting current as the surgeons could. I don't know why dermatologists couldn't treat this case.

DR. ANTHONY C. CIPOLLARO: I should like to discuss this question from two standpoints: First, as to whether acrodermatitis chronica atrophicans should be included among the precanceroses—this is the first such case I have seen, but in talking to other physicians and reading the literature I find there have been several others. Therefore, acrodermatitis chronica atrophicans should be observed for the development of growths such as this. Whoever treats this case undertakes grave responsibility. From the way this tumor is growing out from the surface, I believe the infiltration may go even into the capsule of the joint and the ligaments. In that case, local destructive measures such as electrosurgery or scalpel surgery followed by grafts might not be adequate. I am not sure it is correct to say that patients with anaplastic epitheliomas should not be treated with x-rays. I am not sure that they don't respond. In a lesion as large as this and in this location, conservative treatment would be roentgenotherapy, and radical treatment would be amputation of the leg. I do not favor amputation at this time.

DR. GEORGE C. ANDREWS: Where you have an anaplastic epithelioma of that size, the patient is entitled to a gland dissection of the groin, at least. That is a metastasizing type of tumor, and whether the glands are palpable or not, she should have an inguinal dissection. That fact would make this case one for surgical treatment.

DR. A. BENSON CANNON: I have seen four such cases. The first was many years ago in Dr. Fordyce's office. The patient had extensive acrodermatitis chronica atrophicans with a fungating epitheliomatous growth involving almost the entire extent of the lower part of the right leg. Amputation was performed at the upper part of the thigh, and the patient was still well several years later. I presented a man to this society some 10 or 12 years ago suffering from extensive acrodermatitis chronica atrophicans of many years' standing. There was a large carcinomatous lesion in the affected area on the lower third of the leg. He had an amputation of the leg just below the knee and was still well some five years later. I have always thought that carcinoma was more frequently seen in acrodermatitis chronica atrophicans than in scleroderma, which is a much commoner disease. Moreover, I have considered carcinoma in acrodermatitis chronica atrophicans relatively benign in that such growths appear in already scarred tissue which prevents the rapid dissemination of the new growth. None of the cases I have seen have had a history of irradiation.

DR. WILBERT SACHS: The patient had several ulcers on the other leg, but these healed readily. This ulcer also developed in the acrodermatitis chronica atrophicans but instead of healing went on to form an anaplastic epithelioma. It is a question whether the surgeon, plastic surgeon or dermatologist should treat this lesion. Mohs's method would be an excellent way of treating this case, or possibly the peripheral biopsy method could be used. It is my impression that in a number of cases of anaplastic epithelioma the severity of the process was definitely increased by irradiation. I agree with Dr. Traub that the dermatologist could do as good a job in this case as could the surgeon.

Subacute Disseminated Lupus Erythematosus: Remission after Treatment with Chloramphenicol. Presented by DR. J. GARDNER HOPKINS.†

P. B., a man aged 30, is presented from the Veterans Administration Hospital, Bronx, N. Y. He was first seen on Aug. 22, 1949 with an eruption on the forehead, cheeks, chest, neck and arms, of three months' duration, and a 20 pound (9 Kg.) weight loss. On examination there was a sharply circumscribed, dusky red edematous plaque over the "butterfly" area of the face, with a similar lesion on the forehead. The skin of the ears and neck was erythematous, edematous and covered with white, tenacious scales, with some crusting of the ears and sides of the neck. The lips were slightly swollen and crusted. There were isolated and confluent erythematous papules on the chest, back and arms. Physical examination revealed an otherwise normal condition.

On August 23, the hemoglobin was 14.5 Gm., red blood cells numbered 4,400,000, and white blood cells, 2,750, with 64 polymorphonuclear leukocytes, 23 lymphocytes, 12 monocytes and 1 eosinophil. The platelets were 61,500; the erythrocyte sedimentation rate was 20 mm. per hour, and serum protein, 7.6 Gm. per 100 cc., with 5.1 Gm. of albumin and 2.5 Gm. globulin. The blood urea nitrogen was 16 mg. per 100 cc.; blood culture was negative, and the results of urinalysis were normal.

On March 14, 1950, the hemoglobin was 14.9 Gm., red blood cells numbered 4,800,000 and white blood cells, 3,100, with 45 polymorphonuclear leukocytes, 45 lymphoctyes, 8 monocytes and 2 eosinophils. There were 328,000 platelets; the erythrocyte sedimentation rate was 17 mm. per hour, and results of urinalysis were normal.

Roentgenograms of the chest were repeatedly normal. An electrocardiogram was within normal limits.

Biopsy was reported as showing a picture consistent with acute lupus erythematosus.

The patient's temperature on admission was 100 F., and it gradually rose to 102 F. in 10 days. During this period the patient lost 8 pounds (3.6 Kg.), was extremely nauseated and manifested aphthous lesions of the mouth, erythematous areas on the finger tips and a spread of the papular lesions on the trunk. He was given chloramphenicol, 4.5 Gm. daily, from September 2 to October 6. He also received repeated small blood transfusions, vitamin E (100 mg. three times daily from August 30 to November 15), injections of liver extract and symptomatic, supportive and topical medication as indicated.

† Dr. Hopkins died on Feb. 27, 1951.

The temperature began to drop about September 9 and was normal by September 15. At the same time the lesions on the face and neck subsided with peeling, leaving residual pigmentation. The papular lesions also faded, and by the end of October the skin looked as it does today. The patient had three short bouts of fever after September 15, each one coinciding with a buttock abscess at the site of a liver injection. One of these developed while the patient was still taking chloramphenicol.

This patient, who was acutely ill when first seen, has been practically asymptomatic for about three months. He still has a faint erythema of his cheeks and neck and leukopenia. Whether the remission was spontaneous or due to chloramphenicol it is impossible to state.

DISCUSSION

DR. FRANK C. COMBES: I agree, of course, that this is an instance of remarkable response to treatment with chloramphenicol (chloromycetin®). One unusual feature is the occurrence of this disease in a man. Undoubtedly the bacterium responsible for the production of the disease in this patient is sensitive to this antibiotic. In another patient with the identical dermatosis the treatment might be entirely without benefit. In all probability this man will suffer a relapse. Continuation of the chloramphenicol therapy may eventually cause the pathogen to undergo mutations to such a degree that eventually it will no longer be chloramphenicol-sensitive. I would be interested to hear the eventual fate of this patient.

DR. GEORGE M. LEWIS: In another patient who made a remarkable recovery the remedy which seemed responsible was vitamin E (mixed tocopherols).

DR. WILBERT SACHS: It is interesting to see the number of drugs now being used in this type of case. Dr. Hopkins said that he was not sure about the clinical diagnosis. The microscopic picture is no more than presumptive for the diagnosis as presented. Without knowing anything about the patient, it would be possible for one to say that the condition was a toxic dermatitis, probably an acute or subacute lupus erythematosus type.

DR. FRANK E. CORMIA: We must be careful in attributing improvement to any type of therapy in subacute lupus erythematosus unless the disease is severe at the time of therapy. Even if it is relatively severe, spontaneous remissions may develop. If bacterial allergy is of importance in the development of this disease the response may vary considerably, according to whether there is excessive liberation of bacterial protein, on the one hand, or interference with bacterial symbiosis, on the other. Recently I observed a patient with subacute lupus erythematosus with aggravation by chloramphenicol, this result indicating that the effect of the drug is by no means uniform.

DR. A. BENSON CANNON: Such a dramatic therapeutic result in a usually fatal disease is enough to warrant our questioning the diagnosis. The lesions on the patient's lips and chin are characteristic of the discoid type of lupus erythematosus, and whether the generalized erythema that the patient had was lupus erythematosus or simply a toxic erythema, I am unable to say. The normal determinations for serum protein, albumin and examination of the urine are also against the diagnosis of acute disseminated lupus erythematosus. The patient was given so many remedies that it is impossible to know what made him well. The presenter is to be commended for achieving an apparent cure, regardless of the diagnosis and the remedies used.

DR. HARRY SHATIN (by invitation): We used the various forms of therapy because the man was very ill. He did not begin to show improvement until he received chloramphenicol, but the improvement after that therapy was very rapid. He had been receiving vitamin E for several weeks prior to the use of chloramphenicol, but without improvement. Although it was of no apparent value, vitamin E therapy was continued because of the patient's critical condition.

DR. J. GARDNER HOPKINS: I would just like to make it clear that we are not presenting this treatment as a cure. I thought it might be interesting to show that in one case the condition has responded well, so that perhaps others learning of these results might try this therapy.

Tinea Profunda (Trichophyton Rubrum) of Leg with Improvement on Treatment with Trichophytin. Presented by DR. GEORGE C. ANDREWS.

Multicentric Basal Cell Epithelioma. Presented by DR. A. BENSON CANNON.

A Case for Diagnosis (Pemphigus? Erythema Multiforme Bullosum?): Remission After Chloramphenicol Therapy. Presented by DR. J. GARDNER HOPKINS.

Localized Atopic Eczema. Presented by DR. GEORGE M. LEWIS.

Angioma Treated with Irradiation and Solid Carbon Dioxide. Presented by DR. MAURICE J. COSTELLO.

A Case for Diagnosis: Dermatitis Herpetiformis? Erythema Multiforme? Presented by DR. J. GARDNER HOPKINS.

John C. Graham, M.D., *President*
Anthony C. Cipollaro, M.D., *Secretary*
April 25, 1950

Seborrheic Dermatitis. Presented by DR. J. LOWRY MILLER.

A. R., a woman aged 30, was first seen at Vanderbilt Clinic on April 6 complaining of an erythematous rash on the nose and cheeks which had been present for a year. She had been well prior to that time. There was no itching or scaling. She had consulted a dermatologist, who made a diagnosis of lupus erythematosus and injected bismuth and liver twice a week from May to November. The patient avoided sunlight but thinks the eruption was aggravated during the summer.

During the last three months itching red patches have appeared on the forehead, ears and scalp. These have largely cleared on local therapy since the patient came to the Vanderbilt Clinic three weeks ago. She is now three months pregnant.

There are pea-sized to dime-sized reddish, nonscaling lesions scattered over the bridge of the nose and adjacent areas of the cheeks. There is no evidence of atrophy, follicular plugging or telangiectasia. On the left arm there are a few excoriated papules. There is some generalized scaling of the scalp. The mucous membranes are normal.

A roentgenogram of the chest and a complete blood count were normal. Biopsy showed within the upper part of the dermis an inflammatory infiltration characterized by polymorphonuclear leukocytes, lymphocytes and a few plasma cells. This infiltrate appeared at many points to have a focal arrangement, but it was not that seen typically in lupus erythematosus. Edema and degeneration of the collagen were noted in association with the foci of cellular infiltration. At one point within the epidermis, which was moderately acanthotic, was an area containing degenerating epithelial cells, polymorphonuclear leukocytes and dried serum. This appeared to represent a dry pustule. There was mild hyperkeratosis with considerable parakeratosis. No patulous or hyperkeratotic follicles were present. There was nothing in the sections to suggest lupus erythematosus. The picture was that of a nonspecific dermatitis with a pustule.

DISCUSSION

DR. WILBERT SACHS: It is difficult to make a positive clinical diagnosis. The microscopic pustular lesions appear to be artefacts. An elastic tissue stain may be of some help, for if elastic tissue were found clumped beneath the epidermis that observation would favor the diagnosis of lupus erythematosus, which otherwise could probably be ruled out.

DR. A. BENSON CANNON: † We have been unable to find any evidence of lupus erythematosus in this case, either clinically or pathologically. I am sure that if the lesions were located elsewhere on the body lupus erythematosus would not be suspected. We found only a dry, slightly red and faintly desquamating area. The sparsity of the eyebrows, with redness and fine scaling, as well as the facial lesions, could be allergic in origin.

DR. FRANK C. COMBES: If the patient were presented without the histopathologic diagnosis I feel the majority might have made a diagnosis of lupus erythematosus. The lesions seem too well defined and too persistent to be due to a contactant. I am wondering what the response would be to small doses of roentgen radiation. I have found giving these a good therapeutic test in the differentiation of lupus erythematosus from seborrheic dermatitis. The latter and contact dermatitis should respond promptly.

DR. FRANK E. CORMIA: It is impossible for me to state from the clinical appearance whether the disorder is lupus erythematosus or not, but my impression is that it is not. Both the history and the clinical appearance suggested the possibility of a rather localized form of rosacea. I think it would be worth while trying carbon dioxide slush.

DR. GEORGE C. ANDREWS: I agree with Drs. Costello and Cormia. I believe the condition is a form of rosacea, and I imagine the patient's face and also her cold hands and feet would

† Dr. Cannon died Nov. 27, 1950.

be benefited by the administration of estrogens. It would be wise also to look for Demodex folliculorum because once in a while we encounter a type of rosacea in which that is important, although in most cases it is of secondary significance.

A Case for Diagnosis: Balanitis Xerotica Obliterans? Erythroplasia of Queyrat? Presented by DR. MAURICE J. COSTELLO.
Sarcoidosis with Reticulated Scarring Around the Neck. Presented by DR. LESLIE P. BARKER.
Leprosy. Presented by DR. FRANK C. COMBES.
Delusions of Parasitosis. Presented by DR. EUGENE F. TRAUB.
A Case for Diagnosis: Nummular Eczema? Presented by DR. EUGENE F. TRAUB.
Nevus Flammeus Treated by Tattooing. Presented by DR. ANTHONY C. CIPOLLARO.

MINNESOTA DERMATOLOGIC SOCIETY

R. R. Kierland, M.D., *President*
E. T. Ceder, M.D., *Secretary*
Feb. 24 1950

Erythroplasia of Queyrat with Epitheliomatous Change. Presented by DR. CARL W. LAYMON, Minneapolis.

C. A., a white man aged 46, noticed a small abrasion on the left side of the penis in 1943. It healed rapidly on application of a salve. Again in 1944 and in 1946 a similar area appeared and healed with local treatment. In 1948 a small lesion appeared on the right side and a recurrent lesion on the left side. Biopsies were performed on specimens from both areas. The patient was given 1,500 r of x-rays weekly for three doses to the right side of the penis. No x-ray therapy was given to the lesion on the left side.

There is a 2.0 cm. thin, atrophic scar with telangiectasia at the periphery on the right side of the penis. On the left side of the penis is an erythematous irregular, nontender ulcerated area. There is some induration. No nodes are palpable in the groin.

Serological tests for syphilis gave negative reactions.

Histological sections were shown.

Basal Cell Epithelioma. Presented by DR. CARL W. LAYMON, Minneapolis.

DISCUSSION OF PRECEDING TWO CASES

DR. H. E. MICHELSON, Minneapolis: I do not believe that the boundaries of the condition known as erythroplasia are very sharply drawn. I believe all lesions of the sort to be potentially cancerous and think they should be treated as such. I have had no personal experience with the therapy used by Dr. Sachs, but to me it appears to be merely a form of chemical cautery; therefore, I think we can use any destructive treatment just as effectively. Such terms as Bowen's disease and Queyrat's disease do dermatology no great good. If a condition is what I call precancerous in the obligate sense, the lesion is almost certain to become cancerous and therefore should be eradicated early.

Dr. JOHN F. MADDEN, St. Paul: I think there are two types of erythroplasia; one of them, as Dr. Michelson said, is an example of cancer throughout its course. Another type may be on an inflammatory basis and spontaneously undergoes involution after a period. In one case that I reported a number of years ago the condition disappeared spontaneously after about two years.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I agree with Dr. Michelson that these lesions should be considered cancerous and not precancerous. However, I do believe there is such an entity as Queyrat's erythroplasia. The clinical picture of the red velvet-like, smooth spots is quite characteristic, as is also the histopathologic picture in typical cases. Some years ago I followed up about eight cases of erythroplasia at Jadassohn's clinic, and we found that all of them eventually turned into cancer. In a few cases radical treatment had come too late; therefore, I believe these conditions should be treated as a cancer right from the beginning.

DR. PAUL O'LEARY, Rochester: If the pathologic examination shows that the glands are not involved and if the carcinoma is found to be of a low grade, a partial amputation may be sufficient. If, however, the carcinoma is of the grade 4 type, even though the glands are uninvolved, a complete amputation and radical glandular dissection is indicated.

Ochronosis. Presented by DR. CARL W. LAYMON, Minneapolis.

J. Z., a white man aged 71, acquired a dusky color of the skin of the face, sclera, ears and dorsa of the hands and ankles in 1929. There were also deformed, painful joints. These changes have persisted. There is no history of the ingestion of phenol.

Examination shows a bluish black discoloration of the face, dorsa of the hands and ankles, ears and sclera. The joints of the extremities, hip and spinal column are deformed.

Urinalysis showed the presence of homogentistic acid. X-ray examination of joints showed rheumatoid arthritis.

DISCUSSION

DR. THOMAS B. FITZPATRICK, Rochester (by invitation): This patient presents the fully developed syndrome of alcaptonuria with ochronosis characterized by a triad of symptoms: black urine, pigmentation of the cartilaginous tissue and arthritis.

Alcaptonuria is an inborn error of metabolism in which there is a defect in the amino acid tyrosine. It is considered to be a rare disorder, and there are less than 200 reported cases. It is inherited as a Mendelian recessive trait. The metabolic defect in this disorder is the inability of the person to metabolize homogentisic acid (2,5-dihydroxyphenylacetic acid), which in the normal person is oxidized to carbon dioxide and water. Because of the metabolic block in the alcaptonuric person, homogentisic acid accumulates in the extracellular body fluids. The triad of symptoms is related to the presence of excessive quantities of homogentisic acid in the tissues.

Black Urine.—The urine is of normal color when freshly voided but gradually turns black on exposure to air because of the auto-oxidation and then the polymerization of homogentisic acid to a black insoluble pigment of high molecular weight. Homogentisic acid is a strong reducing agent and will reduce Benedict's solution. As a result alcaptonuric patients are often treated as diabetics until the correct diagnosis is established. The present patient was treated for several years as a diabetic. Homogentisic acid is easily differentiated from glucose because of its lack of optical activity and failure to undergo fermentation reaction.

Pigmentation.—The black pigment from homogentisic acid is formed and deposited largely in the cartilaginous tissue. This pigment is not melanin, since the term melanin should probably refer only to polymerized orthodihydroxy phenyl compounds (Lerner, A. B., and Fitzpatrick, T. B.: *Physiol. Rev.* **30**:91-126, 1950). This patient has the typical sites of involvement (concha, anthelix and tragus of the ears), symmetrical 2 to 3 mm. triangular pigmented macules in the sclera and blue-gray discoloration of the palmar tendons. The skin is rarely involved, and the peculiar blue reticulated areas of pigmentation noted in this patient on the malar area and the dorsa of the hands are unique. In these areas the pigment is deposited in the form of "loops," suggesting that there may have been precipitation around the capillaries in the papillae.

Arthritis.—Ochronotic arthritis involves the vertebral column and may also affect one or more of the larger joints of the extremities. The pronounced kyphosis noted in this patient is an example of the marked deformity which is sometimes present in the advanced stages of this disorder.

Alcaptonuria has never been observed to undergo a spontaneous remission, and all forms of therapy have failed to restore the normal metabolism of homogentisic acid. The defect most probably results from the absence of an enzyme which is normally required for the oxidation of homogentisic acid, which is formed from tyrosine, and the disorder is therefore akin to phenylpyruvic oligophrenia.

Mycosis Fungoides, in Apparent Remission, in a 37 Year Old Woman. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.

M. D., a 37 year old white woman, was well until July 1944, when she acquired pruritic red plaques on her face, right wrist and arm. X-ray therapy was given to lesions of the

right arm, and they gradually disappeared. By the summer of 1947 similar lesions had appeared on various parts of the body. The patient was hospitalized on June 29, 1947, when she noted increasing size and ulcerating tendencies of the lesions along with a general feeling of weakness.

Physical examination revealed a chronically ill woman with large, indurated rose-red, oozing plaques and tumors on the face, arms, trunk, buttocks and legs with central necrosis of most of the lesions. There were enlarged, discrete and nontender axillary inguinal nodes. Laboratory examinations revealed no abnormality except mild anemia and an eosinophil count ranging as high as 21 per cent. The sedimentation rate was 26 mm. in an hour.

Numerous histological examinations of various lesions revealed essentially the same features: a normal or slightly hyperkeratotic and/or parakeratotic epidermis, moderate acanthosis with prolongation and thickening of the rete pegs and a dense cellular infiltrate in the corium, consisting of lymphocytes, plasma cells, polymorphonuclear cells, eosinophils and reticulum cells.

Biopsy of a lymph node revealed normally preserved architecture and a simple reactive hyperplasia.

The patient was given a course of four injections of nitrogen mustard (methyl-bis [β-chloroethyl] amine), with apparent improvement. She was then given 150 r doses of x-rays, usually with 1 mm. Al filtration, to the lesions, which regressed in most cases after one or at most four treatments. A second course of two injections of nitrogen mustard was also given six weeks before her discharge from the hospital on Nov. 1948. Repeated examinations at regular intervals since that time have revealed her to be in good general health. She has had recurrence only in the region of the right wrist, which responded to a single treatment of 150 r of unfiltered x-rays.

Mycosis Fungoides Beginning in the Scalp. Presented by DR. CARL W. LAYMON, Minneapolis.

DISCUSSION OF CASES OF MYCOSIS FUNGOIDES

DR. THEODORE CORNBLEET, Chicago (by invitation): It was gratifying to see that Dr. Laymon started the treatment of M.D. with nitrogen mustard to see what it would do, in contrast with the usual procedure of using nitrogen mustard only after standard procedures become ineffective. Even here, however, the results have not been any happier than in most other cases.

DR. I. FISHER, Minneapolis: The patient's response to x-ray therapy was incomplete. A similar response occurred with the use of nitrogen mustard alone. We then conceived of the idea of giving the patient nitrogen mustard followed by x-ray therapy and found that a better result could be obtained with considerably less irradiation.

Kaposi's Varicelliform Eruption. Presented by DR. E. T. CEDER, Minneapolis.

A white man aged 18 has been subject to recurrent eczematoid dermatitis of the face, neck and cubital areas intermittently since childhood. The eczematoid dermatitis has been quiescent since 1948. About two weeks ago he acquired a cold sore on the upper lip, and three days ago he first manifested disseminated herpetic lesions over the entire surface of the face, ears and neck. These were originally uniform in size and discrete but have rapidly coalesced into weeping, crusting patches. The temperature has not exceeded 100 F. since the onset, and the patient experienced very little malaise. He was placed on treatment with aureomycin, 250 mg. three times daily, 24 hours ago.

ADDENDUM.—All lesions involuted after seven days of aureomycin therapy.

DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul: In vitro studies have failed to demonstrate that aureomycin has any effect on the virus of herpes simplex.

DR. H. E. MICHELSON, Minneapolis: I treated one child with aureomycin, and the condition responded remarkably. There is some evidence that varicelliform eruptions and eczema

vaccinatum are variations of one and the same thing, and this subject warrants further investigation.

DR. CARL W. LAYMON, Minneapolis: Most of you probably have read the preliminary report by Rudolph Baer in the *Journal of Investigative Dermatology* regarding the treatment of generalized herpes with aureomycin. He thought that such therapy was of definite value.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I thought this was a rather interesting case. I agree with the diagnosis, but the condition seems to me a sort of mitigated eruption. The patient wasn't really sick. The history indicates that he had a herpes simplex lesion about two weeks ago and then about 10 or 12 days later the generalized eruption occurred. From what we know about the generalized eruptions in vaccinia infections, we may assume by analogy that this case represents an eruption of generalized herpes simplex mitigated because of the development of some allergy or immunity.

DR. M. G. FREDRICKS, Duluth: With regard to the value of aureomycin in the treatment of this disease, I wish to add the case report of Kaposi's varicelliform eruption in a 16 year old girl who had had atopic eczema all her life. Within 24 hours of the onset of herpes simplex involving her lower lip and associated with very pronounced adenopathy, a severe pustuloerythematous eruption with marked induration quickly developed on her face and within several days spread to involve the ears, neck, dorsa of her hands, flexor surfaces, wrists and, to a minimal extent, the arms, trunk and lower extremities. The eruption was accompanied with high fever, decided prostration and, for several days, delirium. Treatment both with penicillin, in a dosage of 300,000 units given intramuscularly twice daily, and with aureomycin, in a dosage of 250 mg. given by mouth five times daily, was started, without appreciable result. It was not until after three or four days of the patient's hospital stay that the typical picture of Kaposi's varicelliform eruption was present. After a stormy course and a 26 day hospital stay, the patient was discharged. At the time of her admission the atopic eczema was minimal, with involvement of the flexor surfaces of the upper and lower extremities. At the time of discharge her skin was clear. No appreciable effect from either the aureomycin or penicillin was apparent as expressed either in cutaneous lesions or in general systemic involvement.

Palmar Erythema and Onychotrophia. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.

H. L., a 72 year old retired Army sergeant, was admitted to the Medical Service, Minneapolis Veterans Hospital, for epigastric pain. Among other physical findings were noted palmar erythema, said to have been present for 20 years, and extremely soft finger nails with little nail substance remaining. The latter condition had been noted for five years; the toe nails were not involved.

Results of complete x-ray and laboratory studies with the exception of the following observations were within normal limits. Three basal metabolic rate determinations several days apart gave results of +20 per cent or over. Several liver function test results were only slightly abnormal, but sulfobromophthalein retention in 45 minutes was 25 per cent or more on three occasions; cholesterol was 232 to 243 mg. per 100 cc., with esters making up 70 per cent of the total. Liver biopsy revealed moderately severe fatty metamorphosis with questionable early cirrhosis. The patient denies more than very light alcoholic intake throughout his lifetime.

DISCUSSION OF PRECEDING THREE CASES

DR. JAMES R. WEBSTER, Chicago (by invitation): About a year ago I presented at the Chicago Dermatological Society a boy who at birth had a hypertrophic scar in the same area as the defect in the scalp of the baby in the first case. It was interpreted at the result of a congenital defect which had healed in utero. At that time Dr. Oppenheim stated that such lesions were due to amniotic adhesions. These lesions are known to heal rapidly.

DR. CARL W. LAYMON, Minneapolis: This type of congenital defect is rare. It usually is round or oval and most frequently occurs on the vertex, although similar lesions have occurred on other parts of the body, such as the knees. Although they heal rapidly they leave a scar,

and when they occur on the scalp there is always an area of cicatricial alopecia. Some observers have blamed such defects on amniotic adhesions, although there is considerable disagreement on this point.

DR. THEODORE CORNBLEET, Chicago (by invitation): In the case of H. L. only midportions of the nails are involved, pointing up the growth method of nails in longitudinal sections. In this case, one is reminded of Hutchinsonian teeth, in which only the middle radical suffers from dysplasia.

Systemic Blastomycosis with Cutaneous Involvement. Presented by DR. CARL W. LAYMON, Minneapolis.

E. F., a 34 year old white secretary, acquired pain in the upper right portion of the chest in October 1949. Deep breathing, coughing and sneezing aggravated the distress, which has since remained. She has had mild fatigue. On Jan. 20, 1950 she noticed slight discomfort and itching in the lateral aspect of the left upper arm and felt a small nodule. Since then she has acquired other small subcutaneous nodules on the right upper arm and a lesion on the chin. Later, subcutaneous nodules appeared on the sternal region, superior portion of the right thigh, right and left buttocks and the hard palate. The latest lesion is on the lower lip.

The patient had an operation on the right breast in 1941 and one on the left breast in September 1949. In both cases the diagnosis was cystic fibroadenoma.

On the medial aspect of the right arm are three subcutaneous, nontender, freely movable nodules about 3 mm. in diameter. On the hard palate, in the lower lip, in the upper sternal region and on the right and left buttocks are similar discrete, painless nodules. The temperature has been normal at all times.

Laboratory observations were as follows: hemoglobin, 82 per cent; red blood cells, 4,010,000; white blood cells, 9,800 with normal differential; sedimentation rate, 36 mm. in one hour; reactions to serologic tests for syphilis, negative, and Mantoux reaction (1:1,000), negative. A biopsy of the bone marrow showed changes which suggested a mild inflammatory reaction. A roentgenogram of the chest showed a rather dense homogenous infiltration involving the apex and infraclavicular region of the right lung, which was compatible with a diagnosis of blastomycosis. A histologic section was shown from a specimen of the lesion on the right side of the chin.

DISCUSSION

DR. PAUL O'LEARY, Rochester: Has the patient been given skin tests with blastomycin?

DR. ALAN DIXON, Minneapolis: I had tested her and found her not to be sensitive. Systemic blastomycosis is rare indeed, forming from 5 to 10 per cent of the cases. This case presents some interesting features: 1. The patient had chest pains about three months, and it was the presence of the nontender nodules, with the fear of cancer, that sent her to the doctor. This fact makes the incubation period of the disease hard to ascertain. 2. The chest lesion is apical. 3. The wound healed by primary intention and did not suppurate on removal of tissue from the nodules for biopsy.

DR. CARL W. LAYMON, Minneapolis: When I first saw the patient I thought of the following possibilities: tuberculosis, cancer of the lung, sarcoidosis and one of the deep fungous infections. A biopsy was performed on one of the subcutaneous nodules, and Blastomyces was found. The lung is the organ most commonly involved in systemic blastomycosis. Of all cutaneous lesions, nodules beneath the skin are the commonest. The nodules in systemic blastomycosis are frequently furunculoid or carbunculoid but may also begin subcutaneously, as they did here.

Mycosis Fungoides? Presented by DR. S. E. SWEITZER, Minneapolis.
Familial Hemorrhagic Telangiectasia. Presented by DR. CARL W. LAYMON, Minneapolis.
Congenital Ectodermal Defect: Bifid Thumb and Depression in Scalp. Presented by DR. CARL W. LAYMON, Minneapolis.
Pachyonychia Congenita. Presented by DR. S. E. SWEITZER, Minneapolis.
Pityriasis Lichenoides et Varioliformis Acuta. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.
Telangiectatic Nevus. Presented by DR. CARL W. LAYMON, Minneapolis.
Xanthoma Tuberosum. Presented by DR. CARL W. LAYMON, Minneapolis.
Verruca Senilis. Presented by DR. CARL W. LAYMON, Minneapolis.

Schamberg's Disease. Presented by DR. CARL W. LAYMON, Minneapolis.
Purpura. Presented by DR. CARL W. LAYMON, Minneapolis.
Darier's Disease. Presented by DR. CARL W. LAYMON, Minneapolis.
Parapsoriasis Guttata. Presented by DR. CARL W. LAYMON, Minneapolis.
Erythroderma: Psoriasis? Atopic Dermatitis? Presented by DR. CARL W. LAYMON, Minneapolis.
Keratosis Follicularis (Darier's Disease). Presented by the Dermatology Staff of Minneapolis Veterans Hospital.
Linear Scleroderma. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.
Epidermolysis Bullosa (?) Associated with Multiple Myeloma. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.
Pemphigus Vulgaris, in Apparent Remission. Presented by the Dermatology Staff of Minneapolis Veterans Hospital.

MANHATTAN DERMATOLOGICAL SOCIETY

Wilbert Sachs, M.D., *President*
George M. Lewis, M.D., *Secretary*
March 14, 1950

Fixed Drug Eruption Due to Penicillin. Presented by DR. ORLANDO CANIZARES.

S. M., a man aged 24, is presented from the Veterans Administration Hospital, Bronx, N. Y., with a recurrent eruption of the penis. The patient suffered frozen feet and hands in Bastogne and received shell fragments in the face in 1945, after which occurrence he had left-sided trigeminal neuralgia. While returning to the United States in 1945, aboard a hospital ship, he acquired a lesion on the shaft of the penis which was diagnosed as "ringworm." This cleared up with local treatment. On May 6, 1949 he underwent a Caldwell-Luc operation to remove splinters from the left maxillary sinus, after which he was given penicillin daily for four days. On May 8 he manifested an erythematous, vesicular eruption on the shaft of the penis. This cleared up on treatment with saline soaks. On October 4 he had a revision of a scar on the right side of the face and was given penicillin daily for four days. On October 6 he again acquired a pruritic, erythematous, vesicular eruption on the shaft of the penis, and this again subsided. On March 3 he had a revision of a scar, with removal of a hematoma, and again received penicillin intramuscularly. A pruritic, erythematous, vesicular eruption developed on the shaft of the penis. No adenopathy was noted.

The Wassermann reaction of the blood was negative. A trichophytin test gave a positive reaction at a 1:10 dilution. Scrapings and culture were negative for fungi.

Intradermal injection of crystalline potassium penicillin G, 1,000 units per 0.1 cc., elicited no reaction but produced pruritus of the penis in five hours. A similar test with 2,000 units per 0.1 cc. also elicited no reaction, but the patient experienced severe pruritus of the penis in five hours.

DISCUSSION

DR. MAX SCHEER: I am glad to see the patient because I have never seen a fixed eruption from penicillin.

DR. JACK WOLF: It is the first instance of fixed eruption to penicillin that I have seen.

DR. SAMUEL M. PECK: It might be worth while to carry out a test with penicillin ointment containing approximately 5,000 units per gram right near the lesion on the penis. If that elicited no reaction, the ointment could be rubbed directly on the lesion in an attempt to produce a flare.

DR. GEORGE M. LEWIS: It is a very interesting reaction and comparable to the flare-up that may occur on the feet of patients with dermatophytosis.

DR. HERMAN SHARLIT: Is it possible that a contamination of the penicillin, rather than the penicillin itself, is responsible for this eruption? It might be something that would be destroyed in the stomach if the drug were given by mouth.

DR. NATHAN SOBEL: I have seen two patients recently who had bullous eruptions on the wrist following the administration of penicillin. That occurrence has been described previously, although it is rather uncommon, and I think it fits in with fixed eruption, too.

DR. ORLANDO CANIZARES: The first time the presented patient had a lesion of that type it was called tinea by the physician aboard ship. The patient cannot remember definitely whether he had penicillin therapy at that time but thinks he had. Lesions were observed in the surgical

department and called herpes every time (relapsing herpes progenitalis following administration of penicillin), but we feel that this condition is a localized fixed drug eruption. If we can follow Dr. Peck's suggestion we will try a patch test.

Lichen Planus et Acuminatus Atrophicans. Presented by DR. DAVID BLOOM.

M. M., a woman aged 33, was previously presented before this society by the late Dr. Abramowitz, with the diagnosis "Folliculitis Decalvans Associated with Lichen Spinulosus," in January 1942 (ARCH. DERMAT. & SYPH. **45**:1182 [June] 1942) and on April 7, 1942 at the New York Academy of Medicine (ibid. **46**:899 [Dec.] 1942).

DISCUSSION

DR. DAVID BLOOM: It is gratifying to be able to show this patient, who was presented here nine years ago. At that time no typical lichen planus lesions were seen—only lichen spinulosus lesions, follicular pustules, abscesses and alopecia of the scalp. At that time several members, in spite of the biopsy report of lichen planopilaris, thought the condition was not lichen planus but some toxic bacterid. Credit must be given to Dr. Wilbert Sachs, who stated at that time that the patient might later acquire lesions typical of lichen planus.

Dermatitis Due to Grenz Rays. Presented by DR. HERMAN SHARLIT.

S. M., a man aged 43, registered at the Skin and Cancer Unit of University Hospital on Jan. 20, 1950, complaining of an eruption on the hands, of five days' duration. The patient is a physicist at the Police Department, and from January 9 to January 16 he examined, by means of grenz rays, clothing exposed to gun shots. On the seventh day after beginning this work he noticed an inflammation of his hands. When he was seen at the clinic, four days later, his hands, especially the right one, showed pronounced erythema, edema and exfoliation. The factors used were 25 kv., 10 ma., and 18 inches (45 cm.) distance. The grenz ray tube was supplied with a beryllium window.

When the patient was examined on March 10, four days before presentation, the eruption was greatly improved but there was still a distinct erythema of the dorsal aspect of the right thumb, index finger and middle finger and of the areas around the joints of these digits. There was also some suggestion of telangiectasia. The eruption on the left hand was much less severe.

The patient has been hypersensitive to the sun's rays since early childhood, reacting with a vesicular papular eruption on the arms, hands and lips.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: It is shocking for a physicist to expose himself indiscriminately to the beam of grenz rays, knowing that it is the same as that of x-rays and produces the same type of damage. There was enough exposure to produce exfoliation four days later. The intensity of radiation must have been grossly excessive.

DR. MAURICE J. COSTELLO: One of the strong contentions of the proponents of grenz ray therapy is that these rays do no harm. I have seen at one of our clinics several patients with chronic radiodermatitis following grenz ray therapy. One was a child with a cavernous hemangioma in the right deltoid region. I suggested that the vascular nevus be treated with sclerosing solutions. Instead, the patient received many grenz ray treatments. The skin covering the hemangioma is now affected by active radiodermatitis.

Psittacosis with Positive Frei Reaction. Presented by DR. ORLANDO CANIZARES.

J. K., a man aged 38, was admitted to the Veterans Administration Hospital, Bronx, N. Y., on Dec. 27, 1949. Eight days prior to admission, after exposure in a cold storage plant, he acquired a "cold" with rhinitis, dull aching headaches and dry cough. Two days after the appearance of these symptoms he acquired chills and sweats, occurring as often as every two hours and persisting up to admission.

The patient is a bird fancier and keeps parrots, canaries and pigeons as pets. In his work as longshoreman he handles parakeets, parrots, canaries and other birds.

Roentgen examination revealed bilateral basilar pneumonitis. Physical examination showed slight dulness to percussion at both bases posteriorly. There were crepitant rales at both bases with scattered inspiratory wheezes throughout the chest.

Bacteriologic examinations were negative, as were the results of cold agglutination tests and studies for acid-fast bacilli.

The Frei test gave a positive reaction in 48 hours, which rapidly subsided. These results were reproduced on two occasions.

Kahn, Mazzini and Wassermann reactions were as follows:

	Kahn	Mazzini	Wassermann
12-29-49	Positive (10 Kahn units)	Positive	Negative
1-20-50	Doubtful	Positive	Negative
1-24-50	Negative	Positive	Negative
2-28-50	Negative	Negative	Negative

Results of spinal fluid examination were normal on March 6, 1950.

On admission, Dec. 27, 1949, the white blood cells numbered 12,500, with 84 polymorphonuclear leukocytes, 11 lymphocytes and 5 monocytes. On Feb. 1, 1950 white blood cells were 9,800 with 57 polymorphonuclear leukocytes, 29 lymphocytes, 9 monocytes, 3 eosinophils and 2 basophils.

The titer in the lygranum complement fixation test was 1:8,192 on January 17. On February 8 it was 1:2,048.

NOTE.—On April 25 the titer was 1:256.

DISCUSSION

DR. NATHAN SOBEL: A positive Frei reaction is quite common in psittacosis (Hilleman, M. R.: Viruses of Special Interest to the Dermatologist, ARCH. DERMAT. & SYPH. **61**:210-236 [Feb.] 1950). Both viruses concerned are put into the so-called lymphogranuloma-psittacosis group, characterized by particularly large viruses, recognizable in some stages of their development under the ordinary microscope. The complement fixation test is also group reactive, and the results of positive reactions must be evaluated in the light of clinical findings and the patient's history. The agents which comprise the psittacosis-lymphogranuloma group include the viruses not only of psittacosis and lymphogranuloma venereum but also of ornithosis, meningopneumonitis, human pneumonitis (strains SF, Louisiana and Illinois), spontaneous pneumonitis and feline pneumonitis and, finally, the less definitely related viruses of trachoma and inclusion blennorrhea (inclusion conjunctivitis).

DR. ORLANDO CANIZARES: I have not been able to find any references. Dr. Rake could find only his own report. In psittacosis the complement fixation test is used routinely for diagnosis. As for differentiation from lymphogranuloma venereum, in psittacosis the reaction rapidly becomes strongly positive and then goes down whereas in lymphogranuloma venereum it gradually becomes positive and recedes slowly.

DR. JACK WOLF: Psittacosis also responds well to aureomycin therapy.

DR. ORLANDO CANIZARES: The striking thing is that this patient responded well to administration of penicillin, which has been shown experimentally to have some effect on the virus of psittacosis but clinically is not particularly active. I suppose aureomycin therapy could have a good effect.

Necrobiosis Lipoidica Diabeticorum and Granuloma Annulare. Presented by DR. JACK WOLF.
Larva Migrans. Presented by DR. NATHAN SOBEL.
A Case for Diagnosis: Hereditary Keratoderma Palmare? Presented by DR. DAVID BLOOM.
Parapsoriasis Lichenoides Varioliformis. Presented by DR. ISADORE ROSEN.

Herman Sharlit, M.D., *President*
George M. Lewis, M.D., *Secretary*
April 11, 1950

A Case for Diagnosis: Dermatitis Herpetiformis? Senear-Usher Syndrome? Presented by DR. SAMUEL M. PECK.

M. P., a woman aged 64, in January 1948 acquired erythematous, itching patches under the breasts, for which she received various local treatments without improvement. Six months

later she experienced generalized itching, with a vesicular eruption on her arms and lower extremities. Biopsy at that time was reported by Dr. C. F. Simms as showing pemphigus. The patient was hospitalized and given a course of sulfapyridine and later, carbarsone, to which she responded favorably for a short period. Biopsy of a small pigmented lesion on the nose at this time was reported as showing melanocarcinoma. A second, wider excision was performed. The patient gradually acquired infiltrated, scaling, erythematous plaques on the side of the nose which gradually spread to involve more of the face and the scalp and neck. At times these have oozed, and at others they have been crusted and scaling.

The patient's eruption has been controlled on occasion with various drugs, to most of which she has become intolerant. These include penicillin, to which she was desensitized, aureomycin, sulfonamide drugs, suramin (naphuride®) sodium, carbarsone and various antihistamine preparations. These medications had little if any effect on the lesions on the face. At present the patient is receiving potassium arsenite (Fowler's) solution, with injections of diphenhydramine (benadryl®) hydrochloride and suramin sodium.

Results of repeated urinalyses have been normal. The blood count is normal except for secondary anemia and eosinophilia, with a count which has been as high as 16 per cent.

The patient now complains of intense itching and burning pain in the lesions on the face. The eruption on the body is not causing her much concern. On the face in patches and on the scalp and neck are scaling plaques, sharply demarcated and dusky, with some telangiectasia. On the arms and legs are excoriations, with scarring and pigmentation, and occasional small vesicles.

DISCUSSION

Dr. Paul Gross: Another instance of transformation of a generalized bullous eruption into a Senear-Usher syndrome was presented at the March meeting of the New York Academy of Medicine. The patient had been seen several years before by Dr. Cannon with a generalized bullous eruption typical of pemphigus; at the time of the Academy meeting localized lesions as seen in pemphigus erythematosus were present. I believe considerable change has taken place in the clinical course of the entire group of bullous diseases since the introduction of the sulfonamide drugs and antibiotics. My impression is that some of the cases of erythema multiforme pemphigoides have been adversely affected by penicillin therapy. The phenomenon described by Milian as biotropism, consisting in an increased virulence of a penicillin-resistant virus because of the temporary suppression of penicillin-sensitive bacterial flora, might provide an interpretation for that occurrence.

Dr. Wilbert Sachs: When a Senear-Usher syndrome is fully developed, do you consider it pemphigus or something else?

Dr. Maurice J. Costello: I think this patient has pemphigus erythematosus, as the presenter stated, and I can well understand how the eruption could be confused with lupus erythematosus. I recall a patient who had pemphigus erythematosus diagnosed as bullous lupus erythematosus, with most of the involved areas on the exposed surfaces, who acquired pemphigus vulgaris and died of that disease.

Dr. Wilbert Sachs: I agree with the diagnosis as presented, although I have never seen dermatitis herpetiformis develop into a Senear-Usher syndrome. In that event it may behave like ordinary pemphigus.

Dr. Max Scheer: My impression is that this patient has pemphigus vulgaris.

Dr. Herman Sharlit: I am intrigued by the possibility of what these antibiotics can do to bullous diseases. We have been seeing things that are a little unusual, and how to evaluate them at this time I don't know. We must watch the relationship between the treatment we give and what develops afterwards.

Dr. Samuel M. Peck: The question, I think, was really well put by Dr. Sachs—was the case one of benign pemphigus to begin with, or can we have a Senear-Usher syndrome in Duhring's disease?

Calcinosis Cutis. Presented by Dr. Nathan Sobel.

R. J., a boy aged 10, was first seen at the Skin and Cancer Unit on March 22, 1950 with an eruption of seven years' duration. On the inner aspect of the left leg just below the knee there

is a pea-sized hard superficial nodule with a yellowish tinge. There are also numerous shotty, hard subcutaneous, skin-colored nodules in linear arrangement in the anterior axillary lines of both axillas and also in the right cubital fossa and the popliteal areas.

Results of urinalysis and the hemogram were normal. The biopsy specimen was diagnosed as showing calcinosis cutis.

DISCUSSION

DR. GEORGE M. LEWIS: It is unusual to see calcinosis cutis in linear formation, but on palpation it is seen that the lesions fit in very well with that diagnosis.

DR. DAVID BLOOM: Calcinosis of metabolic type, to which this case belongs, is usually manifested in a different way than in this case: It is located mostly on the elbows and knees or along the tendons and over the joints of the hands, forming raised lesions which have a tendency to break down and discharge whitish material. The calcium content of the blood and other chemical observations are usually normal. There is frequently a history of preceding illness, such as nephritis, necessitating a long stay in bed. I assume that this preceding illness is the cause of changes in metabolism which lead to calcium precipitation. In this case the mother states that the eruption appeared when the child was 3 years old, after an attack of possible poliomyelitis.

DR. WILBERT SACHS: The clinical picture is not typical of calcinosis cutis, but the histologic picture is.

DR. SAMUEL M. PECK: Has the child received massive doses of vitamin D?

DR. DAVID BLOOM: The mother denies that the boy has had any illness and any special medication since the age of 3, except the above-mentioned attack of possible poliomyelitis.

DR. HERMAN SHARLIT: Any real elucidation of this case would involve a thorough examination. It doesn't look right on simple inspection.

DR. NATHAN SOBEL: I agree with what has been said. The parathyroid glands have been accused in some of these cases. The Suttons in their textbook reported that they thought the condition was due to diminished parathyroid secretion.

Scleredema Adultorum. Presented by DR. JACK WOLF.

R. K., a woman aged 57, is presented from the Skin and Cancer Unit, New York University-Bellevue Medical Center, with solid edema of the neck, upper extremities and upper part of the trunk, of one year's duration. We were unable to elicit any history of acute illness preceding the onset. The patient gave a history of nervousness and of tremor of the hands for the past 17 years.

She presents induration of the arms and the cheeks, the nape of the neck, shoulders and upper part of the chest. There is no pitting on pressure. The skin is smooth, taut and cannot be readily picked up between the fingers. There is restriction of the normal motion of the neck and upper extremities as a result of this involvement. To some degree the involvement of the cheeks gives the patient's face a masklike expression.

The basal metabolic rate, blood count and results of urinalysis were normal. The erythrocyte sedimentation rate was 20 mm. per hour. Serologic tests for syphilis gave negative reactions.

Histologic examination by Dr. A. B. Hyman confirmed the clinical diagnosis of scleredema.

DISCUSSION

DR. MAX SCHEER: I think the diagnosis is correct. In the few cases I have seen there has always been a history of infection, such as influenza, which antedated the eruption. This patient gives no such history.

DR. PAUL GROSS: I am inclined to agree with the diagnosis but would still remain on the alert to the possibility of the infiltrative stage of scleroderma.

DR. DAVID BLOOM: I agree with the diagnosis. A similar patient was treated by me some time ago with injections of hyaluronidase on the assumption that the edema of the skin was due to an increase of hyaluronic acid. The injected areas became soft and stayed so for about 48 hours, but thereafter the hardness reappeared.

DR. WILBERT SACHS: Although there are features of scleroderma I believe the disorder is scleredema adultorum. Such cases are rare. It is difficult to make a microscopic diagnosis of scleredema adultorum, for there is no characteristic picture. It is an edematous process and may easily be confused with other dermatoses.

Lichen Planus and Leukoplakia. Presented by DR. JACK WOLF.

R. K., a woman aged 42, is presented from the Skin and Cancer Unit with an eruption in the mouth of approximately two years' duration. She stopped smoking about three months ago, but prior to that she smoked about 20 cigarets daily.

The patient presents three different types of lesions in the mouth. On the left buccal mucous membrane she has a well developed, leukokeratotic, firm, raised and even somewhat roughened patch about 1 by 3 cm. in size, lying transversely. On the right buccal mucous membrane she presents annular bluish white lesions characteristic of lichen planus. The tongue is most unusual; it is covered with small, bluish white and even somewhat yellowish flat papules, matchhead sized, which impart a cobblestone-like effect to the tongue's surface.

Histologic examination of the lesion on the left buccal mucous membrane revealed the picture of leukoplakia. No report has as yet been made on the specimen removed from the tongue.

Serologic tests for syphilis gave negative reactions.

DISCUSSION

DR. NATHAN SOBEL: I would rather make one diagnosis and call the entire condition lichen planus. I know that the keratotic lesion doesn't show that picture histologically, but it might on a different biopsy.

DR. MAX SCHEER: I think the whole thing is lichen planus. I recently had a patient with severe involvement of the buccal mucosae, hard palate and tongue, with extensive hyperkeratosis. My original diagnosis was leukoplakia, but the behavior, recurrence and disappearance made me suspicious. Dr. Sachs studied the biopsy and reported typical lichen planus. I think Dr. Wolf's case in its entire picture is lichen planus, and I suggest another biopsy.

DR. GEORGE M. LEWIS: From the clinical features there are two conditions in the mouth, and I agree with the presenter.

DR. SAMUEL M. PECK: Under the Wood light leukoplakia fluoresces and lichen planus does not.

Poikiloderma Vasculare Atrophicans, Probably Due to Mycosis Fungoides: Ichthyosis Vulgaris. Presented by DR. PAUL GROSS.

Lichen Planopilaris. Presented by DR. GEORGE M. LEWIS and DR. WILBERT SACHS.

Malum Perforans, Healed with Aureomycin Ointment. Presented by DR. MAURICE J. COSTELLO.

A Case for Diagnosis: Periarteritis Nodosa? Eosinophilic Granuloma? Presented by DR. SAMUEL M. PECK.

A Case for Diagnosis: Parapsoriasis Guttata? Pityriasis Rosea? Presented by DR. HERMAN SHARLIT.

Paraffinoma. Presented by DR. SAMUEL M. PECK.

A Case for Diagnosis: Bullous Lupus Erythematosus? Lupus Erythematosus Complicated by Dermatitis Venenata Simulating Recurrent Herpes Simplex? Presented by DR. DAVID BLOOM.

Leprosy. Presented by DR. MAURICE J. COSTELLO.

CHICAGO DERMATOLOGICAL SOCIETY

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April 19, 1950

Lichen Nitidus with Koebner's Phenomenon. Presented by DR. M. EBERT, DR. V. LEAF and (by invitation) DR. D. MUSGRAVE.

DISCUSSION

DR. M. J. BRUNNER: At Illinois we had a typical case of lichen nitidus, proved by biopsy, in which was exhibited the Koebner phenomenon. In each scratch mark on the leg one could see typical lichen nitidus papules. Three months ago, in the *Proceedings of the Royal Society*

of Medicine, in the discussion of a case of lichen nitidus, there was some comment by one or two of the discussers to the effect that the Koebner phenomenon in lichen nitidus is not rare.

In two cases which were presented from Cook County Hospital the Koebner phenomenon was also present.

Blastomycosis. Presented by Dr. D. Omens and (by invitation) Dr. H. Omens and Dr. D. Musgrave.

DISCUSSION

Dr. Oliver S. Ormsby: From 1901 to 1903 this disease was at its height, and in 1903 I first saw a systemic case. Before seeing this I had cultures in my laboratory from 100 different patients. The patient with the systemic case was in a south side hospital and was supposed to have tuberculosis. This patient had deep and superficial ulcers and nodules of quite generalized distribution. We could demonstrate the blastomycosis organism microscopically without difficulty. After the patient's death a postmortem examination was made at the hospital. The internal organs, including the liver, spleen and lungs, together with the skin and bones, were all occupied by large numbers of micro-organisms. The doctor who performed the autopsy contracted the disease, but he later recovered.

In the last few years there have been fewer cases. Numbers of patients were seen from 1901 to 1903. During the work at that time I had more than 100 cultures growing in the laboratory. These were all thrown onto the concrete floor one night by a monkey I kept in the laboratory. It did not take long to replace them. While at present the disease is not common there are enough patients to keep us familiar with the disorder.

Xanthomatosis Tuberosum Multiplex with Endocrine Anomaly. Presented by Dr. Theodore Cornbleet, Dr. D. Cohen and (by invitation) Dr. D. Musgrave.

DISCUSSION

Dr. Hamilton Montgomery, Rochester, Minn.: This patient had xanthomatosis for 15 years. It started in adolescence, and he is now 32. In the juvenile forms of xanthomatosis one sometimes sees a combination of xanthoma tuberosum and xanthoma disseminatum. Dr. Weidman some years ago recorded such a case in which there was pituitary disease. This boy had lesions in the axilla and fine lesions on the upper arm which would fit in with the picture of xanthoma disseminatum, which is a relatively rare condition. There may be associated diabetes insipidus, and some patients have Hand-Schüller-Christian disease. This condition is not necessarily associated in any way with cretinism.

Dr. Theodore Cornbleet: This man has much in him of the cretin, but I think that term does not fully describe him. There are elements of pituitary dwarfism present, and it is intriguing to think of the xanthomatous infiltrates scattered about elsewhere as also involving the pituitary gland or hypothalamus. This involvement could reduce the amount of thyrotropic hormone and a consequent hypothyroidism follow.

Molluscum Contagiosum, Not Responding to Treatment with Aureomycin Hydrochloride. Presented by Dr. Theodore Cornbleet, Dr. D. Cohen and (by invitation) Dr. S. Barsky.

DISCUSSION

Dr. A. L. Welsh, Cincinnati, O.: My associates and I have had six molluscum contagiosum patients on treatment with aureomycin for three weeks in much larger doses than were given to this boy. They were not benefited.

This patient presents an example of the Koebner phenomenon. We had a patient who had hundreds of scratches, and every scratch was studded with molluscum contagiosum lesions. I recently saw a patient who had a lesion on the palmar surface of the middle phalanx of the right fourth finger. A surgeon removed the lesion, and the pathologist reported it as a pacinian corpuscle neuroma. It recurred six weeks after the initial surgery. It was excised again, and the pathologist again reported it as a neuroma. It was removed again, and the surgeon grafted the

area. The lesion recurred at the edge of the graft. It was a typical single lesion of molluscum contagiosum. Review of the sections of the earlier lesions revealed molluscum contagiosum papules cut tangentially.

This disease can occur in very atypical forms.

DR. STEPHEN ROTHMAN: In connection with the Koebner phenomenon I should like to recall the classic experiment of the late Viennese virus expert, B. Lipschutz. He infected chicks with subclinical doses of fowl pox virus intravenously. These doses were too small to elicit the pox eruption. However, by traumatizing the skin Lipschutz provoked the eruption at the site of trauma. I think there is good reason to suspect virus etiology in all instances in which the Koebner phenomenon is observed, including psoriasis and lichen planus.

Hodgkin's Disease with Severe Pruritus. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

DISCUSSION

DR. STEPHEN ROTHMAN: I should like to confirm the statement that adenylic acid has no value whatsoever in the symptomatic treatment of pruritus, either in Hodgkin's disease or in any other condition.

DR. ADOLPH ROSTENBERG JR.: We saw no effect from adenosine-5-monophosphate (my-b-den®) in eight cases carefully studied in the hospital.

DR. S. W. BECKER: I know of several patients who received adenylic acid with no relief of itching.

A Case for Diagnosis: Lichen Ruber Moniliformis? Presented (by invitation) by DR. SHELDON A. WALKER and DR. SIDNEY STEINBERG.

DISCUSSION

DR. OLIVER S. ORMSBY: I do not believe this disorder is lichen ruber moniliformis, which is a rare disease. The lesions have a budlike arrangement, and they are quite hard, and although they suggest that disease clinically I do not believe the condition is that disease. I am not sure about the histological picture, but I feel that in a histological section lichen ruber moniliformis will not be found.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Wise and Rein had an exhibit at a meeting of the American Medical Association many years ago, and I had the opportunity of studying their sections of lichen ruber moniliformis. The histopathological changes in the present case do not fit such a diagnosis. The histopathological picture in lichen ruber moniliformis looks more like that of neurodermatitis. The histological observations in this case are of pyknosis of cells in the epidermis and pronounced increase in pigment in the epidermis and in the lymph nodes. The changes in the cells in the epidermis are similar to those seen in arsenic pigmentation. The patient handles fruit and thus may come in contact with arsenic. In this case I would also think of drug eruption from other heavy metals and/or quinacrine. It is true that the patient presents linear lesions similar to those described in Wise and Rein's case and similar to the picture from Dr. Hyde's case which is in the Ormsby and Montgomery text. The histopathological changes in this case suggest more a neurodermatitis and do not show any features of lichen planus. I am unable to make a definite diagnosis.

DR. M. R. CARO: I cannot offer a definite diagnosis, but the case did not suggest lichen ruber moniliformis to me. It might well be a case of disseminated lupus erythematosus, for there were present both atrophy and plugging of the follicles in many of the lesions.

DR. SHELDON A. WALKER: I should like to thank Dr. Montgomery for his suggestion of arsenical dermatitis. We will investigate this possibility further.

In line with Dr. Caro's suggestion that this might be an atypical lupus erythematosus, it is interesting to note that McFarland (ARCH. DERMAT. & SYPH. **55**:674-687 [May] 1947) found collagen changes in lichen ruber moniliformis similar to those occurring in lupus erythematosus.

Multiple Papillomas, Presented by Dr. E. A. Oliver and Staff, the Department of Dermatology, Veterans Administration Hospital, Hines, Ill.

C. H., a 56 year old Negro, has had about 40 gray-black pedunculated, cauliflower-like lesions up to 6 cm. in diameter on the trunk, genitalia, buttocks and thighs since the age of 13, which up until three to four years ago caused him no particular concern. He states that since that time the lesions have increased several times in size and occasionally have become irritated and itchy. There is no history of similar lesions in other members of his family.

Routine laboratory studies revealed essentially normal conditions.

Biopsy report on one of the lesions was as follows: There was some parakeratosis, pronounced acanthosis and papillomatosis, hyperpigmentation of the entire epidermis and a mild to moderate inflammatory infiltrate in the superficial portion of the dermis with dilatation of the blood vessels.

DISCUSSION

Dr. S. W. Becker: This is an unusual picture, although it has been reported before. I believe these are benign epidermal neoplasms, which I do not think will ever become malignant. They could be removed very easily.

I would not call them nevi with no nevus cells. Similar lesions which are called epidermal nevi are simply benign epidermal neoplasms. Unna called them nevi; he called seborrheic warts seborrheic nevi. The nomenclature of these lesions is most confusing. In the famous case reported by Wolff (*Arch. Dermat. u. Syph.* **47**:417, 1899), Pautrier and Hugel (*Bull. Soc. franç. dermat. et syph.* **29**:81, 1922) and Pautrier and Levy (Transactions, Congrès des dermatologists et syphilographes de langue française [Strasbourg, 1923], Paris, Masson & Cie, 1925, p. 386) there were hundreds of tumors on the body which had appeared at about the age of 4. The patient was presented in one of the German dermatological meetings as having bizarre acanthosis nigrans. He had multiple benign papillomatous tumors. The carcinoma from which he died seemed to be at least contiguous to one of these tumors but probably did not arise from it.

Dr. Julius E. Ginsberg: Most of these lesions have been present for a great many years. The microscopic structure is consistent with condyloma acuminatum. The papillomatosis, the acanthosis and the mild infiltrate are consistent with that diagnosis. The odor that occurs in the genital lesions is almost consistently present in condyloma acuminatum.

The L. E. Phenomenon. Presented by Dr. J. H. Mitchell.

Subacute Disseminated Lupus Erythematosus. Presented by Dr. M. H. Ebert and (by invitation) Dr. B. Yaffe.

A 17 year old white male student was admitted to Presbyterian Hospital with the chief complaint of a rash on the face for two months. He had been in good health when he first noticed a small erythematous lesion on the right side of his nose. During the next month this gradually spread to form a butterfly-like pattern over the cheeks and nose, and since then the condition has remained stationary. The eruption has been entirely asymptomatic, and the patient has continued to feel well.

In the past he has had measles, and in 1940 he was hospitalized for two months for rheumatic fever. He has since been followed in the cardiac clinic with only minimal changes found. His activities have not been restricted. There is no previous history of skin disorders or venereal disease.

The family history is noncontributory except that his mother had an arrested case of pulmonary tuberculosis.

The physical examination revealed a well developed, healthy-appearing young man. The major observations were a "butterfly" erythematous rash over the cheeks and bridge of the nose, with some involvement of the forehead, left ear and a few small patches on the hard palate. There was moderate generalized lymphadenopathy. The heart was not enlarged, but soft systolic and presystolic murmurs were heard. The chest and abdomen were normal.

Laboratory tests revealed hemoglobin of 10.5 Gm., an erythrocyte count of 3,540,00 and a leukocyte count of 5,100. There were 57 per cent neutrophils, 40 per cent lymphocytes and 3 per cent eosinophils. The sedimentation rate was 55 mm. per hour uncorrected. The urine and stool

were normal. The reaction to the Kahn test was 4+, and in the Wassermann test was anticomplementary. Determinations on blood chemistry were as follows: carbon dioxide capacity, 48 volumes per cent, and 36 mg. nonprotein nitrogen, 110 mg. sugar, 632 mg. sodium chloride, and 7.35 Gm. total protein with 4.25 Gm. albumin and 3.10 Gm. globulin per 100 cc. The Hanger test reaction was 3+ in 48 hours, and the heterophil antibody test gave negative reactions. The patient had no sulfobromophthalein retention and his excretion of phenolsulfonphthalein was normal. The reaction to the tuberculin test was positive. Roentgenologic examination of the chest showed enlargement of the left auricle, and an electrocardiogram was normal.

DISCUSSION OF PRECEDING TWO PRESENTATIONS

DR. F. E. SENEAR: I am interested to see this disease in a male, when the usual preponderance of cases is in women. My associates and I now have two men in the hospital with subacute lupus erythematosus; the preceding lupus erythematosus patient there was a male, and the patient presented by Dr. Ebert is a young man.

I was struck last week when giving the Board examinations to see a boy only 5 years of age with a picture much like this on the face and with lesions on the extensor surfaces, elbows, knees and other joints and on the dorsal surface of the fingers. Everybody made a diagnosis of disseminated lupus erythematosus in spite of the fact that the boy had a relatively good involvement of the upper eyelids. The boy was unable to lift himself from the table. The condition was a classic case of dermatomyositis. The interesting thing was the weakness of the muscles, which had appeared only two weeks before we saw the patient. A diagnosis of lupus erythematosus had been made by his physician, who had not seen him after he manifested the weakness. It behooves us not to overlook the possibility of dermatomyositis in a case resembling lupus erythematosus.

DR. JOHN F. MADDEN, St. Paul: Dr. Mitchell should be complimented on the excellence of his exhibit, which was assembled in such a short time. The point Dr. Senear brought out is shown in the exhibit, namely that the L. E. cell is not demonstrated in dermatomyositis. The L. E. cell has been found in other diseases; therefore, it has lost a certain degree of diagnostic value. The L. E. cell has been found in cirrhosis of the liver, leukemia and multiple myeloma. So far the L. E. phenomenon has been produced only in patients who have *acute* lupus erythematosus.

DR. THEODORE CORNBLEET: Walker and Benditt in Dr. Rothman's laboratory found the gamma globulin of a normal level in dermatomyositis. My associates and I were able to corroborate their observation. Since the gamma globulin is high in lupus erythematosus, the difference in levels of this serum protein can be of value as a differentiating measure. Of course, it cannot be compared at all in importance with the finding of L. E. cells as a definitive procedure.

DR. JAMES H. MITCHELL: Some time in February I received a letter from Dr. Weiss in St. Louis saying he had a new test for the L. E. phenomenon and asking me to send any blood I had from a case of lupus erythematosus. I promptly sent it to him when the patient whose case I presented here came in. He then sent the smear preparation, about which he was quite enthusiastic. Dr. Hass and other staff members looked at the smear with a great deal of care. The pathologists were unable to find the significant cells. Dr. Weiss's technic, as you have seen in the *Journal of Investigative Dermatology,* consists in using the white cells of a normal person combined with the serum of the patient, allowing the mixture to stand for a half hour and then staining the smear with the Giemsa technic. I am sure he has other fine preparations, but on this patient the preparation was not good. I talked to Dr. Madden, and he advised me to send the blood to Dr. Haserick, who sent back some beautiful preparations. His technic consists in using bone marrow of the dog. The other boy (the patient presented by Dr. Ebert) has been in the outpatient clinic for a time, and I sent his serum to Dr. Haserick, who promptly returned the smear which you saw today. We have two positive observations in cases which are highly suggestive of lupus erythematosus.

The boy whose picture I presented today is now in the hospital. He came in three weeks ago very sick, and his count had gone down to 1,900.

I think it is very interesting, as Dr. Senear pointed out, that the two cases in the hospital are both in males between 15 and 17 years of age; together with Dr. Senear's cases they make a very interesting group.

DR. M. H. EBERT: The interesting thing is that the boy presented here is not sick. His highest temperature has been 99 and leukocyte count 4,500. He has some edema, but it is not pronounced. He does have what we believe to be a false positive Wassermann reaction. He has generalized adenopathy. He shows the phenomenon of the L. E. cell. It was my understanding that that was found only in acute disseminated lupus erythematosus, but here is a boy who has lupus erythematosus, probably subacute, but it is very early, he is not ill, and the reaction to the cell test is positive. I think this is a real test for the phenomenon, because if the disorder turns out to be an acute disseminated case in an unusual fashion we will know that the L. E. phenomenon is observed very early in the course of the disease.

Acanthosis Nigricans, Probably Juvenile Type. Presented by DR. MALCOLM SPENCER (by invitation).

DISCUSSION

DR. STEPHEN ROTHMAN: This is a typical case of juvenile acanthosis nigricans. Data are accumulating that this condition is due to a primary pituitary disorder, somewhat similar to Cushing's syndrome. It possibly might have something to do with the pituitary growth hormone. In my experience the juvenile form is truly benign and never ends with internal malignant changes.

A Case for Diagnosis: Bowen's Disease, Shaft of Penis? Presented by DR. JAMES H. MITCHELL.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The sections revealed all the features of Bowen's disease or squamous cell epithelioma *in situ* together with vacuolization of some of the cells suggesting the possibility of an arsenical causation. There is no history of ingestion of arsenic. This lesion might be called a dry form of leukoplakia. I would simply call it a squamous cell epithelioma *in situ* as the lesion does not present the clinical features as originally described by Bowen.

DR. FREDERICK BECKER, Duluth, Minn.: I agree with the diagnosis. In addition, I feel that the patient presents definite evidence of arsenical keratoses of the palms and soles. He denies ingestion of any arsenic. However, he is a heavy smoker, and some years ago Dr. E. Dudley Smith recorded arsenical eruptions in patients consuming large amounts of tobacco. Perhaps tobacco is the source of arsenic for this patient.

Lichen Planopilaris? Presented by DR. M. EBERT, DR. V. LEAF and (by invitation) DR. D. MUSGRAVE.
Annular Lichen Planus with Pityriasis-Rosea-Like Distribution. Presented by DR. H. RATTNER, DR. H. RODIN and (by invitation) DR. S. BARSKY.
Tuberculosis Cutis (Erythema Induratum?). Presented by DR. M. EBERT, DR. V. LEAF and (by invitation) DR. D. MUSGRAVE.
Generalized Myxedema. Presented by DR. JAMES R. WEBSTER, DR. S. BLUEFARB and (by invitation) DR. S. BARSKY.
Metastatic Malignant Growth, Primary Site Unknown. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.
A Case for Diagnosis: Pemphigus? Presented by DR. M. EBERT, DR. V. LEAF and (by invitation) DR. D. MUSGRAVE.
Acute Gouty Arthritis with Tophi. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.
Lead Poisoning with Lead Lines on the Gingivae. Presented by DR. JAMES S. WEBSTER, DR. S. BLUEFARB and (by invitation) DR. S. BARSKY.
Vogt-Koyanagi Syndrome and/or Congenital Syphilis. Presented (by invitation) by DR. SHELDON A. WALKER.
Blastomycosis? Dermatitis Medicamentosa Due to Bromides? Presented by DR. F. E. SENEAR and Staff.
Circumscribed Scleroderma, Saber Blade Type. Presented by DR. JULIUS E. GINSBERG and (by invitation) DR. JONAS E. SCHREIDER.
Linear Lupus Erythematosus (Chronic Discoid)? Presented by DR. H. HAROLD RODIN.
Linear and Circumscribed Scleroderma. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. SIDNEY STEINBERG.
A Case for Diagnosis: Angiosarcoma of the Scalp with Hypernephroma? Presented by DR. DAVID COHEN.
Schamberg's Disease. Presented by DR. F. E. SENEAR and Staff.
Epithelioma Adenoides Cysticum. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. BEN FIRESTEIN.
A Case for Diagnosis: Dermatitis Herpetiformis? Pemphigus? Behcet's Triple Symptom Complex? Presented by DR. DAVID COHEN and DR. THEODORE CORNBLEET.
A Case for Diagnosis: Urticaria Pigmentosa? Juvenile Xanthoma? Presented by DR. F. E. SENEAR and Staff.
Sarcoid Reaction at Site of Trauma. Presented by DR. E. A. OLIVER and Staff.
Acrodermatitis Chronica Atrophicans. Presented (by invitation) by DR. SHELDON A. WALKER.
Von Recklinghausen's Disease. Presented by DR. E. A. OLIVER and Staff.
Generalized Leukoderma. Presented by DR. E. A. OLIVER and Staff.
Atypical Granuloma Annulare in Siblings; Combination with Linear Scleroderma in One Case. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. RICHARD B. STOUGHTON.

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*Linsell, W. D., and Fletcher, A. P.: British M. J. 2:1190 (Nov. 25) 1950.

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**Ellis, Calvin C., Wooldridge, Wilfred E., and Weiss, Richard S.: The Journal of Investigative Dermatology, Vol. 10, No. 6, June 1948*

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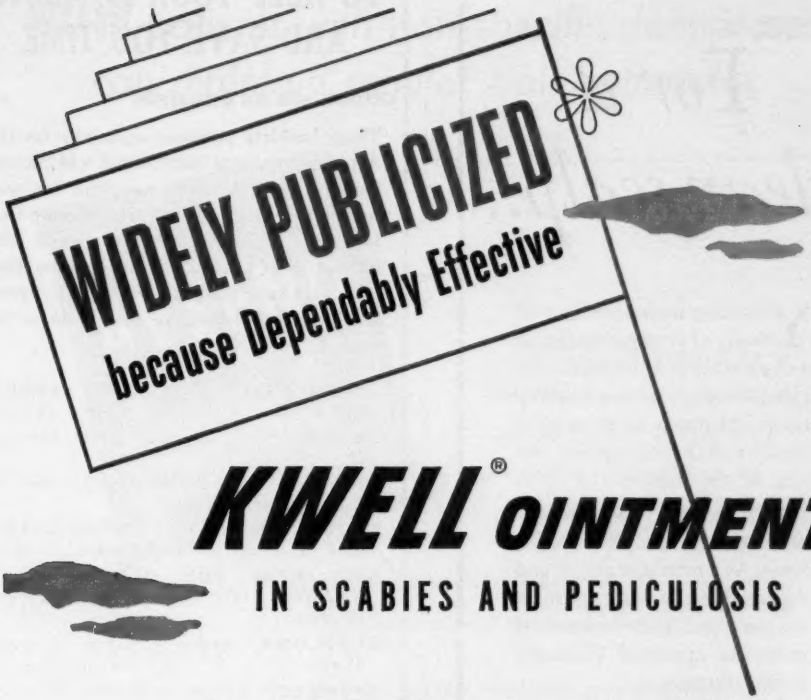

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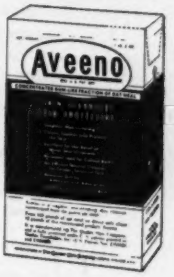

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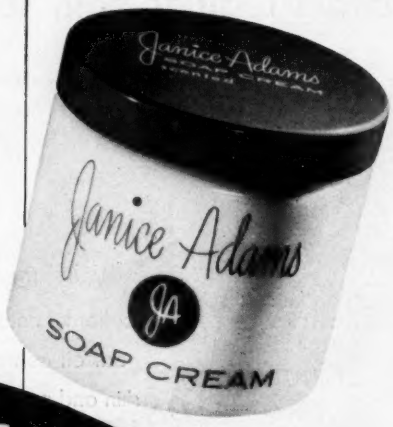

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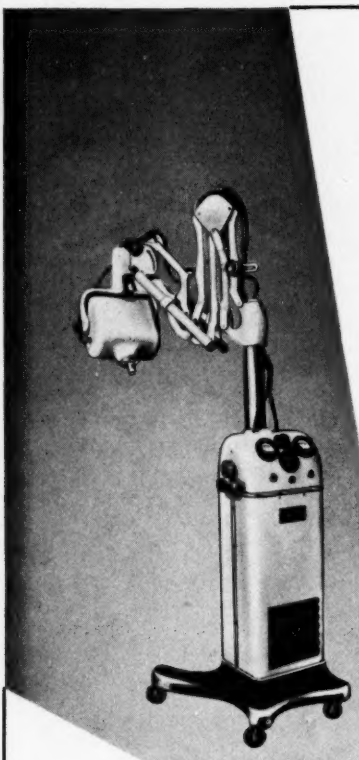

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